Handbook of Herbal Formulation

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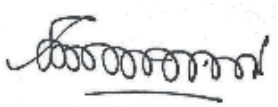
Foreword

The drugs from indigenous system of medicine, particularly herbal formulation modern drugs for preventive and curative purposes worldwide. The herbal formulations are considered to be safe as they consist of herbs or processed herbs to provide specific medicinal, nutritional or cosmetic benefits. The market is flooded with the products that are basically of herbal origin. In this paradigm shift the herbal formulations gained attention and witnessing an enormous escalation in demand in the national and international markets. Herbal products are substituting the synthetics products, as they are not having sharp biological activity and adverse effects. Herbal products are in gigantic demand in the developed world for healthcare as they are considered efficient, safe and have lesser side effects.

The present book is a sincere effort to address different issues associated with the formulation of modern dosage forms containing herbals. I believe that this book will be a connecting tool between traditional and modern dosage forms and would be useful to those who are working in this area. The handbook covers the area of intellectual property rights and patenting of herbal formulations, nutraceuticals, cosmeceuticals, bioavailability of herbals and pharmacovigilance of herbal medicine. The book will be useful to entrepreneurs, manufacturers of herbal products who can effortlessly extract the relevant formulation and process from the handbook.

I am sure this book will be useful to all stakeholders of pharmacy profession.

I congratulate the authors for this manuscript and wish all success for their endeavors.



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Preface

Handbook of Herbal Formulation is the result of abundant hard work of the authors. They have given entire details, right from what this actually means its impetus; the formulation development involved for applying herbs and its various benefits. The book highlighted on the herbs, its formulations and knowledge of traditional and modern pharmacognosy which can stand as a pillar for all postgraduate and undergraduate pharmacy students. The book provides entire details on various evolving topics of herbal formulation and highlighted its gravity.

In view of all-inclusive information of the subject, a textbook is engrossed to give determined pronounce of pharmacognosy. This modern version of herbal formulation emphasizes on definition, classification, herbal excipient, formulation development, conventional dosage form novel drug delivery, intellectual property rights and patenting of herbal formulations, nutraceuticals—herbal-based formulation, cosmeceuticals—herbal-based cosmetic preparation, evaluation of quality, efficacy and safety of herbal formulation, status of herbal formulation, bioavailability of herbals and pharmacovigilance of herbal medicine. The highlighted portion of the text focuses on general introduction to herbal formulation, presents scope and future prospects. In addition, it includes herbal drugs commonly used for formulation developments. The objective of the authors is fully achieved by systematic assemblage of the well-written chapters with neat and clean well-labelled diagram whenever necessary.

The authors convey deep sense of gratitude to their grandparents, parents and son to deeply motivating them to provide a kind of book required for undergraduate, postgraduate and researchers.

Doubtless authors are indebted to all who have supported in giving the present shape to the book.

Last but not least, the authors express heartfelt gratitude towards Mr YN Arjuna for his support, guidance and cooperation to publish this book.

Suggestions and criticism will always be solicited by the authors to further improve the quality of book in real sense.

Sapna Malviya

Neelesh Malviya

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Unit I

Introduction to Herbal Formulations

CHAPTER 1

Herbal Formulation

DEFINITION

Herbal drug formulation is defined as dosage form consisting of one or more herbs or processed herb(s), herbal preparations quantified to provide specific nourishing and beautifying benefit to diagnose, treat, mitigate diseases of human beings or animals and/or to alter the structure or physiology of human beings or animals. Herbal drug formulations are the means by which plant drug or preparation or isolate is delivered to sites of action within the body through topical, parental, nasal, and ophthalmic routes of administration.

Different herbal formulations are extracts, granules, tablets, emulsions, ointment, tinctures, juices and exudates. The herbal substances subjected to various methods like extraction, distillation, expression, fractionation, purification, concentration or fermentation include comminuted or powdered to obtain herbal formulation. Whole, fragmented or cut plants, plants parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh were used in the preparations of herbal formulations. Herbal substances are precisely defined by the plant part used and according to the taxonomical classifications (Fig. 1.1).

AYURVEDIC FORMULATIONS

Ayurveda, the "science of life," or longevity, is more than 5,000 years old holistic alternative science from India. Ayurveda often called **Mother of all Healing** and is aimed at the physical, mental and spiritual wellbeing of human beings. According to tradition, Ayurveda is one of the great gifts of the sages of ancient India to mankind, the teachings of Ayurveda were recollected by Brahmā, the Lord of Creation, as he awoke to begin the task of creating the universe. It stems from the ancient Vedic culture and was taught from many thousands of years in an oral tradition from accomplished masters to their disciples. Ayurveda is the original contribution of India

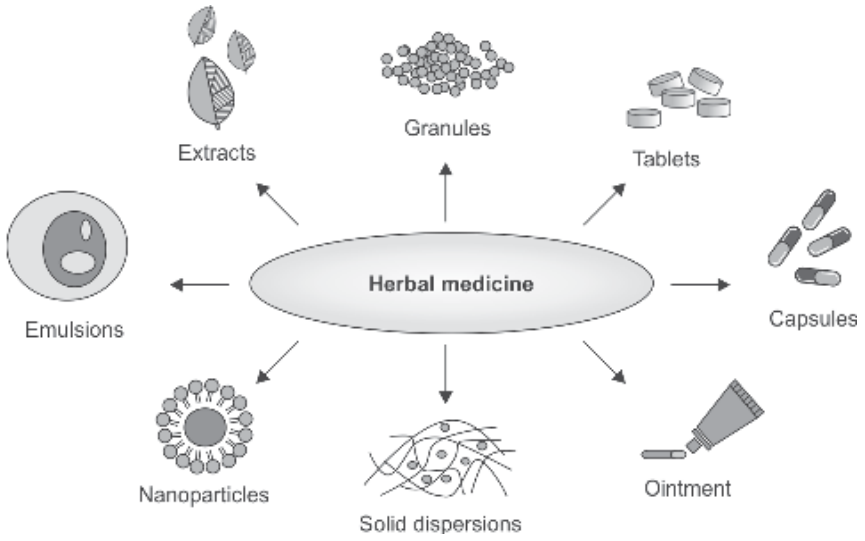


Fig. 1.1: Herbal drug formulations

(Bharatha) to the world and treats man as a whole, which is a combination of body, mind and soul. Ayurveda transcends the period of this universe, stretching beyond the concept of time itself, having no beginning and no end. Brahmā taught this knowledge to *Daksa Prajapati* (the protector of all beings), whom in turn taught it to the *Asviný Kumaras* (the twin holy physicians), who in turn taught it to *Indra* (King of the Gods). Ayurveda is a complete medical system. It places a great emphasis on prevention and encourages maintenance of health in all its aspects; physical health, mental balance, spiritual well-being, social welfare, environmental considerations, dietary and lifestyle habits, daily living trends, and seasonal variations in lifestyle, as well as treating and managing specific diseases. Ayurveda teaches respect for nature, appreciation of life and the means to empower the individual. It is holistic medicine at its best. *Ayurveda* is one of the Indian traditional medicinal systems with well-recognized history for centuries based on philosophy of preventing unnecessary suffering and living a long healthy life. It involves the usage of natural elements to eradicate the root cause of the illness by restoring balance and creating a healthy lifestyle to prevent the recurrence of imbalance, it is combination of *ayu*r (life) and *veda* (science or knowledge), which means "the science of life mainly focusing on bringing harmony and all areas of life including spirit, mind and body. Ayurveda is based on *Panchamahabhutas* or the five elements: *Vayu* (air), *Teja* (fire), *Aap* (water), *Prithvi* (earth) and *Akasha* (aether) which build up the living microcosm (human beings) and the macrocosm (external universe). When pooled collectively in pairs, the *Panchamahabhutas* form *Tridosha* or the three humors, namely *Vata* (responsible for body movement), *Pitta* (responsible for bodily chemical reactions such as metabolism and temperature) and *Kapha* (responsible for growth, protection, lubrication and sustenance).

Types of Ayurvedic Formulations

1. **Classical Ayurvedic Medicines:** Traditional ayurvedic textbooks as Charaka and Sushruta Samhita contain the procedural information and formula to formulate these preparations.
   Examples: Ark, Asava, Aristha, Ghrita and Bhasma, etc.
2. **Proprietary Medicines:** These types of medicines are also known as modern ayurvedic medicine or patent medicines.

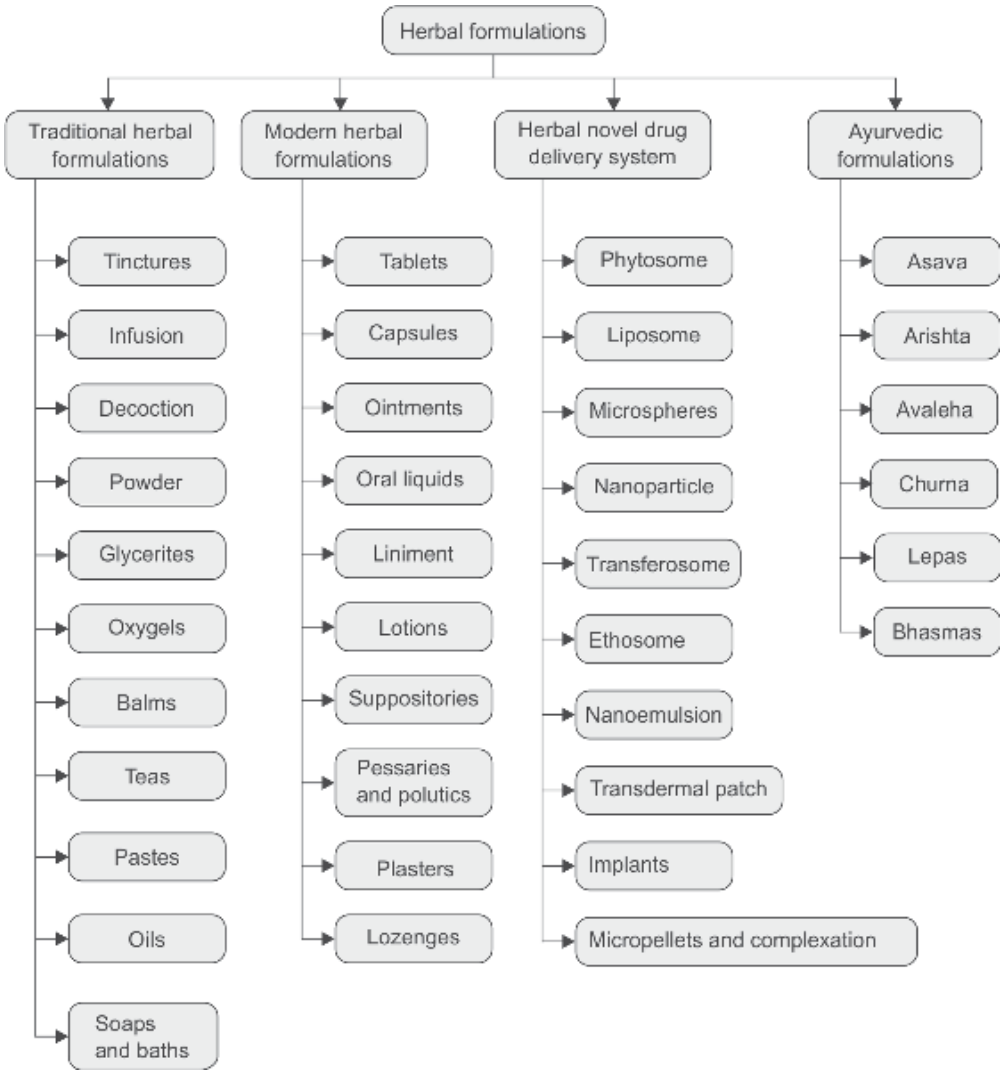


Fig. 1.2: Classification of herbal formulations

The ingredients used to prepare such medicines are not available in ayurvedic textbooks. The manufacturing company decides its formula, mode of preparation and dosage form.

Examples: Syrups and capsules.

The ayurvedic formulations are described as follows:

Ark: These are obtained by distillation of herbs. It is light in nature and very easy assimilated in system. Distillation has not much to do with solubility but rather vaporization points. It allows a volatile substance to be separated from a non-volatile substance.

Asava and arishtas: Asava is ayurvedic preparations prepared with natural fermentation using sugar, water and herb, whereas arishta is prepared by herbal decoctions. These preparations have longer shelf life. The main difference between two is involvement of heat.

Asava and arishta are unique liquid dosage forms that contain self-generated alcohol. Former is made with decoctions of herbs in boiling water while later is prepared by

directly using fresh herbal juices or decoction to undergo fermentations. Arishtas are classical Ayurvedic preparations typically used as digestive and cardiotonic. The arishta (fermented decoction) and asava (fermented infusion) are considered as a unique and valuable therapeutics in ayurveda, due to their medicinal value, sweet taste and easy availability.

Asava–Arishta formulations are better known as hydro-alcoholic formulations, self-generated alcohol during this biomedical fermentation process can reach in between 4–12% v/v, and due to its improved aromatic properties and palatability, these formulations have better patient acceptability. These traditionally fermented formulations have several merits over other Ayurvedic medicines, as self-generated alcohol has better preservation quality.

Preparation of Asava is carried out by Hima (cold decoction)/Jala, Swarasa (expressed juice) process. In the preparation of Asava the drug is coarsely powdered and added to water, to which the prescribed quantities of honey, jaggery/sugar are added. It contains dilute solutions of the readily soluble constituents of crude drugs. Arista is prepared by soaking the drugs in water for a period of time (8 hours) before decoction, which facilitates the better extraction of active principles into kasaya (decoction) and thereby increase in potency. It involves boiling of crude drugs in a specified volume of water for a defined time period. Then it is allowed to cool and filter. This decoction is called "quath" or "kwatha". For kwatha preparation, the percentage of water depends upon the nature (hardness) and quantity of the drug. The ratio of crude drug to water is generally 1:4 or 1:16. During boiling the volume is reduced to one-fourth of its original volume. Then, the concentrated extract is filtered and used as such or processed further. Kasaya is transferred to Sandhana patra and sugar, jaggery or honey is added to it followed by fermentative agent and Prakshepa dravya.

Benefits of Asava–Arishta Formulations

1. Self-generated alcohol and hydrolyzing enzymes released by yeasts aids extraction of phytochemicals from raw herbals.
2. Self-generated alcohol gives pleasing organoleptic properties and dramatically improves palatability of the preparation.
3. Palatability improvement ensures patient compliance and hence clinical outcome.
4. Alcohol is considered as "Yogvahi" meaning facilitate faster and even distribution of drug in body.
5. Self-generated alcohol improves bio-availability of drug molecules.
6. Self-generated alcohol acts as a preservative, Asava–Arishta preparation lasts for several years, without special storage conditions.
7. Preservation benefits availability of herbs independent of seasonal availability of the botanical drugs.
8. Microbial transformation may reduce toxicity of phyto ingredients.
9. Microbial transformation increases chemical diversity in the formulation, which is crucial for its clinical action over the raw drug.
10. Biochemical transformation makes the drug available in its metabolized or activated form, which translates into quick action.

Examples: Dasamoolaarishtam, Amruthaarishtam, Kutajaarishtam, Draakshaarishtam Abhayaarishtam, Balarishtam, Devadaarvaarishtam, Asokaarishtam, Jeerakaarishtam Khadirashtam, Karpoorasavam, Pippalyaaadi asavam, Punarnavaasavam, Usiraashtam Aravindaarishtam, Patrangaasavam.

Avaleha or Lehya: Avaleha or Lehya is a semi-solid preparation of drugs prepared by the addition of jaggery or sugar candy and boiled with prescribed drug juices decoction. Honey, if required, is added when the preparation is cold and mixed well. Ghee or oil is added when preparation is hot. The Lehya should neither be hard nor a thick fluid. When pulp of the drugs is added and ghee or oil is present in

the preparation, this can be rolled between the fingers.

These preparations generally have:

1. Kasaya or other liquids,
2. Madhur Dravya (sweetening agents) like jaggery, sugar, sugar candy and honey
3. Prakshepa Dravyas (additives): These are herbals added to the Avaleha to increase its potency, palatability or to improve organoleptic properties. There are two types of Prakshepa Dravya: Kasthoushadhis (herbal) and Rasoushadhis (metallic).
4. Powders or pulps of certain drugs,
5. Sneh Dravyas (fats) like ghee, oil.

Method of Preparation

1. Jaggery, sugar or sugar-candy is dissolved in the liquid and strained to remove the foreign particles and boiled over a moderate fire.
2. It should be removed from fire, when pressed between fingers it becomes thready (Tantuvat), or when it sinks in water without getting easily dissolved.
3. Powdered drugs are then added in small quantities and stirred continuously to form a homogeneous mixture.
4. Ghee or oil is added and mixed well.
5. Finally, honey is added when the preparation becomes cool and mixed well.

Storage: The Lehya should be kept in glass or porcelain jars. It can also be kept in a metal container which does not react with it. Normally, the Lehya should be used within one year.

Examples: Dashamulaharitaki, Bilvadileha, Vasavaleha, Citraka Haritaki, Chyavanaprasa, Kusmandaka Rasayana, Vyaghri Haritaki, Kalyanaka Guda, Ashvagandhadi Lehya, etc.

Tailas: Tailas are also known as medicated oils forming a group of drugs in ayurvedic system of medicine with the principle is to extract the therapeutic compounds into oil.

Preparation: The method of preparation requires heating of oil with prescribed kashayas (decoction) and Kalkas (powdered drugs) according to formula. They are generally used for Abhyanga (external application). It consists of:

1. Drava [any liquid medium as prescribed in the composition]
2. Kalka [fine paste of the specified drug]
3. Sneha Dravya [tailas]
4. Gandha Dravya [perfuming agents]

The medicated Tailas will have the odour, color and taste of the drugs used in the process. If a considerable amount of milk is used in the preparation, the Tailas will become thick and may solidify in cold seasons. Tailas are preserved in good quality of glass, steel or polythene containers. These medicated preparations retain the therapeutic efficacy for sixteen months.

Examples: Mahanarayana taila, Ksheerabala taila, Dhanwantaram tailam, Maharaja Parsarini Taila, Bhringaraja Taila, Anu-taila.

Churnas

Churna is defined as a fine powder of drug or drugs in Ayurvedic system of medicine. Drugs mentioned in Patha, are cleaned properly, dried thoroughly, pulverized and then sieved. The Churna is free flowing and retains its potency for one year, if preserved in airtight containers. The Churna consisting of fine powder of herbs in appropriate ratio was subjected to standardization by means of various physical, chemical and microbiological methods.

Storage: The packed materials should be stored in cool, dry and dark conditions.

Preparation: Churna is prepared by drying ingredients. These dry ingredients are powdered by using crusher of grinder type. These powders in exact proportions are blended together in stainless steel cone blender.

After testing these are filled in glass/plastic containers.

Examples: Hingwashtaka Churna, Talisadi Churna, Dashamoola kashaya Churna, Sarshapadi Churna, Ajamodadi Churna,

Jatiphaladi Churna, Pushyanuga Churna and Narasimha Churna.

Standardization of Churnas

It generally involves the following parameters:

1. Determination of sieve size
2. Loss on drying/moisture content
3. TLC
4. Total ash
5. Acid-insoluble ash
6. Water-soluble ash
7. Extractive value in water, alcohol and other solvents
8. Phytoconstituents
9. Microbial contaminations
10. Heavy metal limit test for mercury, arsenic, cadmium, and lead
11. Microscopic analysis

Lepas

Lepas are semi-solid preparations intended for external application to the skin or certain mucous membranes for emollient, protective, therapeutic or prophylactic purposes where a degree of occlusion is desired. They usually consist of solutions or dispersions of one or more medicaments in suitable bases. The base should not produce irritation or sensitization of the skin, nor should it retard wound healing; it should be smooth, inert, odorless, physically and chemically stable and compatible with the skin and with incorporated medicaments. The proportions of the base ingredients should be such that the ointment is not too soft or too hard for convenient use. The consistency should be such that the ointment spreads and softens when stress is applied.

Standardization of Lepa

- Loss of drying
- Ash values
- Extractive values
- pH
- Thin layer chromatography

Examples: Dosaghna Lepa, Dasanga Lepa, Sinduradi Lepa and Pathyadi Lepa.

Ghrita

Ghrita are preparations in which ghee is boiled with prescribed Kasayas (decoction) and kalkas of drugs according to formulation as per ayurvedic formulary.

Also known as Snehkalpa. It solidifies on cooling and takes color, odor and taste of ingredient used for preparation. These are preparations of internal composition which remain stable for sixteen months.

Examples: Brahmi ghrita, Asoka ghrita, Sukumara ghrita and Nirgundi ghrita.

Goggulu

Ayurvedic medicines prepared by the exudates, and obtained from the plant *Commiphora mukul*, are known as Goggulu. There are five different varieties of Goggulu in Ayurvedic Shastra but usually two varieties, mahiskasa and kanaka are preferred for medicinal preparation. Exudates in small pieces are taken in a piece of cloth and boiled in gomutara or Dugdha or Triphala kasayua until the exudates pass into the fluid through the cloth to the maximum. The fluid after filtering is boiled till it forms a mass. After drying, the mass is formed into a paste by adding ghee till it becomes waxy.

Rasa Rasayan

Ayurvedic medicines containing mineral drugs as main ingredients are called Rasa rasayan or Ras-yoga. They are in pill form or in powder form/forest, minerals such as Anrala, Swarna, Rajata, Tamra, etc. and sulphur impurified state is used to convert bhasma form, called kajuali, then other drugs are added in small quantities, mixed well and grounded to form fine powder.

Vati or Gutika

Medicines prepared in the form of tablets or pills are known as vati or gutika, these are made of one or more drugs of plant, animal or mineral origin.

Examples: Pranda Gutika, Lasunadi Gutika, Marma Gutika, Sankha Vati and Sanjivani Vati.

Bhasmas

The Bhasmas are the powder of substances obtained by calcinations. The preparation of Bhasmas include following stages:

1. Purva Karma: Sodhana (purification).
2. Pardhana Karma: Marana (incineration/calcination).
3. Paschat Karma: Amritikarna, Lohitikarna.

Sodhana (Purification)

It is prepared from purified minerals, metals, marine and animal products. The following changes are observed: After purification, the materials become free from impurities and become fine as well.

Second Stage (Marana)

The purified drug is mixed with Kasaya of drugs, and it is ground with mortar and pestle for specified period of time. The cakes are prepared and their size and thickness depends on heaviness of the drug. The cakes are dried on the sunlight and placed in Sarava (shallow earthen plate) and closed with other plate and sealed with clay smeared cloth and dried. The pit is dug in open space and sealed plates and cow dung are filled in the pit. Fire is put on all the sides and when burning is over, allowed to cool. The earthen pot is removed and seal is opened and contents are taken out. The medicine is ground into fine powder in a Khalva (mortar and pestle). The process of triturating is repeated as many times for proper finess and quality.

Examples: Gold (Swarna) Bhasma, Mukta Shouktic Bhasma, Mandura (iron) Bhasma and Copper (Tamra) Bhasma.

TRADITIONAL HERBAL FORMULATIONS

Tinctures

Tinctures are normally alcohol and water extracts of plant materials dissolve more easily in a mixture of alcohol and water than in pure water. The preparation of tinctures by maceration of herbal parts in water-ethanol solutions results in the extraction of many structurally diverse compounds with varying polarities. There is the added advantage of the alcohol in a tincture being a preservative, allowing the extract to be kept for several years. The alcohol content of the finished extract needs to be at least 20%v/v to adequately preserve it. Most commercially produced tinctures have a minimum alcohol content of 25% v/v recommended for water-soluble constituents like tannins, mucilage and certain flavonoids and some saponins, while an alcohol concentration of 45–60% v/v is required for alkaloids, essential oils, some glycosides and most saponins, and 90% v/v alcohol for resins and oleoresins. The use of the right ethanol concentration is important in maximizing the quality of the herbal preparations. When kept properly, most tinctures have a shelf life of around five years (Fig. 1.3).

Fennel Tincture

Fennel seed tincture (1:5, 60% alcohol)	3 parts
Licorice root tincture (1:5, 50% alcohol)	1 part

15–30 drops as needed for acute gastritis or simple dyspepsia.

Respiratory Tincture

Red root	4 parts
Myrrh	2 parts
Bayberry	2 parts

Make from the individual tinctures, add 5% glycerin. Take ½ teaspoon in 2 tablespoons of hot water, gargle well and swallow every 2 hours.

Immune Stimulant

Echinacea root	4 parts
Red root	3 parts
Myrrh gum	2 parts
Capsicum	1 part

Antidepressant Tincture

Hypericum (fresh)	6 parts
Aralia Berries (fresh)	5 parts

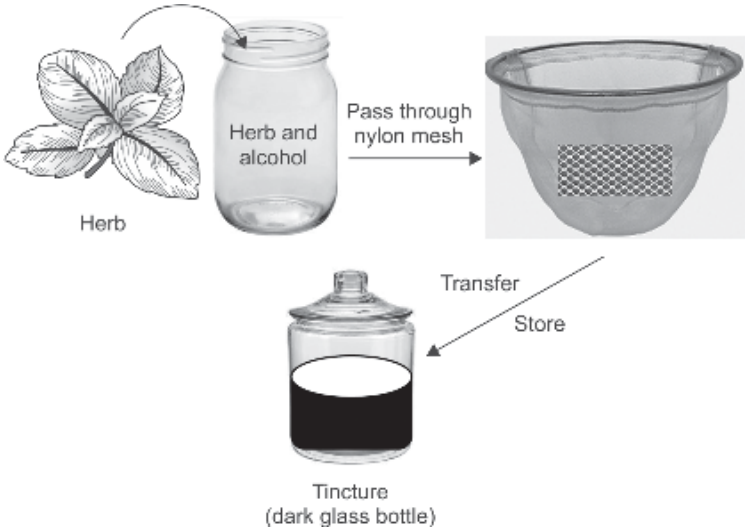


Fig. 1.3: Diagrammatic representation of preparation of tincture

Licorice root	4 parts
Oplopanax (fresh)	2 parts
Panax quinquefolium	1 part

Mix as tinctures. Dose: 60–90 drops up to four times a day. For morbid depression with congestion and dry mucosa.

Infusion (Fig. 1.4)

Infusion is the process of extracting chemical compounds or flavors from plant material in a solvent such as water, oil or alcohol, by allowing the material to remain suspended in the solvent over time. Fresh infusions are prepared by macerating the crude drug for a short period of time with cold or boiling water. These are dilute solutions of the readily soluble constituents of crude drugs.

GASTROINTESTINAL FORMULATION

Laxative Tea

Psyllium seed	3 parts
Liquorice	3 parts

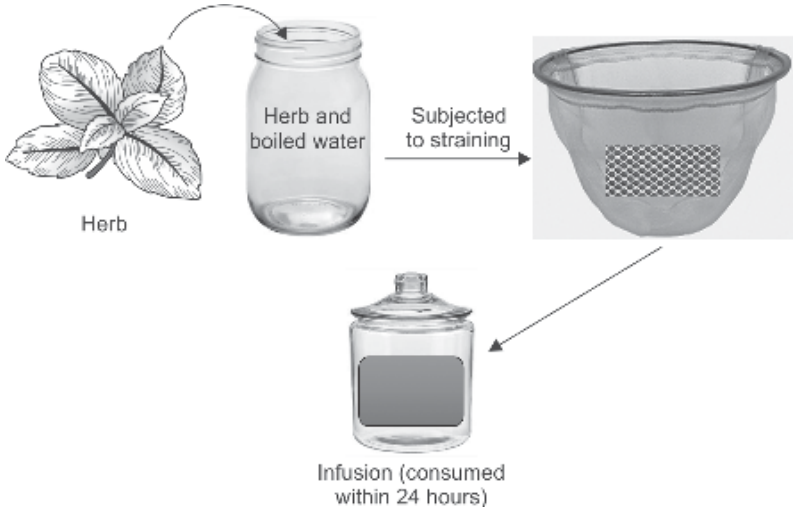


Fig. 1.4: Diagrammatic representation of preparation of infusion

Rhubarb root	2 parts
Senna pods (crushed)	2 parts
Angelica root	2 parts

Drink as a simple infusion in evening.

Stomach Tea

Star Anise	3 parts
Ginger root	2 parts
Papaya leaf	2 parts
Fennel seed	2 parts
Chamomile	2 parts
Comfrey leaf	2 parts
Peppermint (or Poleo)	2 parts
Angelica or Calamus	1 part

As a simple infusion as needed for dyspepsia or mild gastritis.

Decoctions (Fig. 1.5)

These preparations are prepared by boiling the herb in water for specific time to extract soluble constituents out of it. The process mainly done with hard plant materials like bark and roots. The water decoction of a mixture of 2–12 herbal materials is the commonest traditional herbal dosage form. Decoctions are normally intended for immediate use, ideally within a 24-hour period, with about a 72-hour maximum limit if stored in a very cool place. The decotions are mainly preserved by addition of preservatives to avoid spoilage.

In addition, various syrup or honey may be used as sweeteners. In this case, the stability of the preparation should be conducted to determine the shelf-life of the product at a particular storage condition. The concentration ratios of major active components found in the individual herbs were different from those in the decoction indicating the influence of the decocting process in the difference in the amount of active components.

Formulations

Glycyrrhiza glabra (Licorice) root. Strong decoction, used in sodium retention.

Smilax (*Sarsaparilla*) root and rhizome. Cold infusion or strong decoction.

Senna Pods: 1–2 gm, fresh ginger: 1 gm, used in constipation.

Withania somnifera, root, 10 gm, used to relieve stress.

Powders

Powders are finely divided powders that contain one or more plant drugs or dried extracts with or without auxilliary substances including, where specified, flavouring and coloring agents. They are simple to prepare,

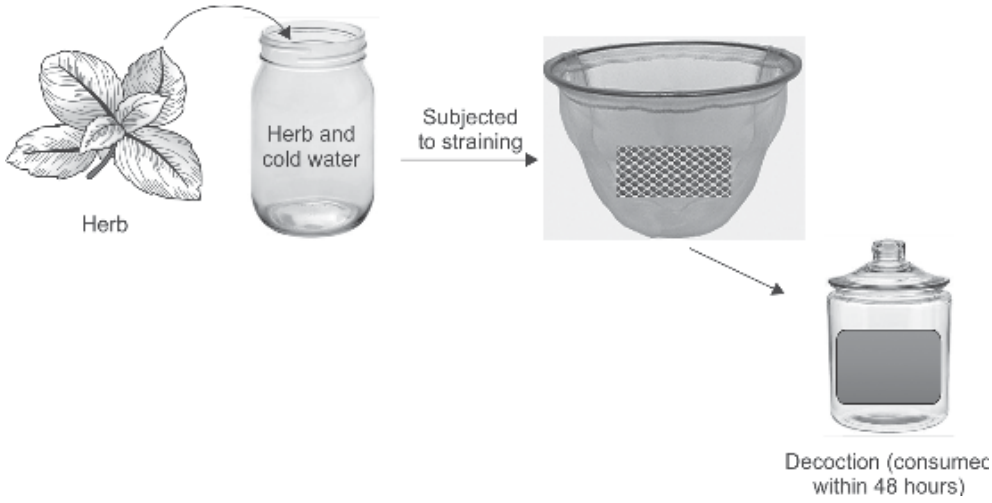


Fig.1.5: Diagrammatic representation of preparation of decoction

less perishable than decoctions, rapidly absorbed, and fast acting. They are intended to be taken internally with or without the aid of water or any other suitable liquid. Patient compliance is better with powders than with decoctions because they are easier and faster to prepare. Powders contain the whole herb; therefore, patients rely on good digestion to break down the herbal matter to release the active constituents. Powders require a smaller dose, generally, than is prescribed for most decoctions. This is due to the type of conditions, typically functional, treated with powders, and because more of the active ingredients are released due to the increased surface area of powders compared to bulk herbs. Also, there is less binding of constituents and less damage to heat sensitive compounds as happens with the prolonged boiling of decoctions.

Powders may be single dose or multiple dose preparations. For single dose powders, each dose is enclosed in a separate container, e.g. a sachet, a paper packet or a vial. With multiple dose powders it may be necessary to provide a measuring device capable of delivering the quantity prescribed. These are preparations that come as powdered herbal materials meant for direct use or by incorporation into foods, beverages for drinking, insufflations, and wounds. They may be finely sifted herbal materials from various parts of plants meant for a particular therapeutic effect. The stability of the powder depends on the type and nature of the herbal material as well as the moisture content of the powder in the bags and packaging (Fig. 1.6).

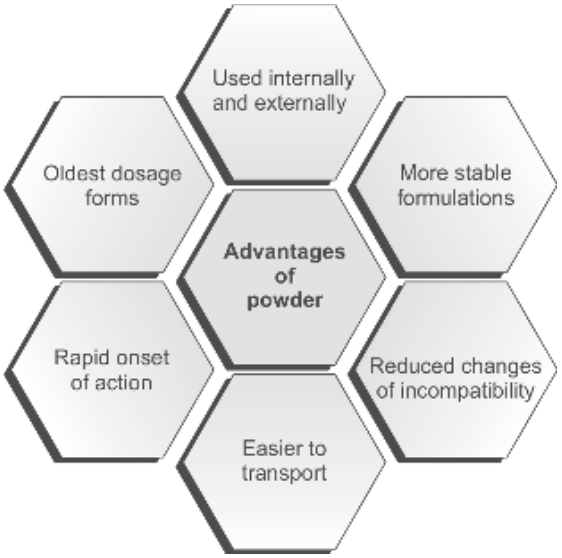


Fig. 1.6: Advantages of powder

Preparation of Powder

In the manufacture of powders, means are taken to ensure a suitable particle size with regard to the intended use of the product. Plant materials or extracts are dried and pulverized into uniform particle size separately and mixed appropriately as per prescribed formula. The precaution should be taken during manufacturing, packaging, storage and distribution of oral powders by suitable means to ensure microbial quality. Store in containers protected from moisture.

Quality Control Tests for Powder

1. Particle size and shape determination
2. Surface area
3. Density: Bulk density, true density and granular density
4. Granule strength and friability
5. Flow properties: Angle of repose, percentage compressibility and Hausner's ratio
6. Moisture content
7. Percentage fine
8. Uniformity of content
9. Uniformity of weight

Herbal Glycerites (Fig. 1.7)

Fill a clean jar with clean, chopped fresh plant material, glycerites are sweet herbal tinctures, which use vegetable glycerin to extract the active constituents and flavor from an herb. Glycerites are made like tinctures only difference is that glycerine is used in the extraction process in its place of a mixture of alcohol and water. A glycerite is kept till concentration of glycerine is at least 50% to 60% in the finished product. Glycerites have a shelf life of approximately one to two years if stored in a cool, dark place. Glycerine is a good preser-

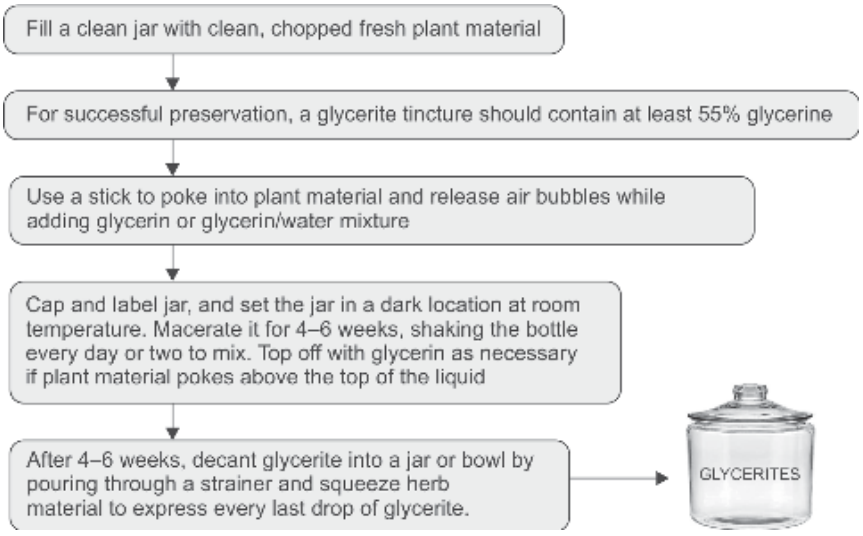

Fill a clean jar with clean, chopped fresh plant material
For successful preservation, a glycerite tincture should contain at least 55% glycerine
Use a stick to poke into plant material and release air bubbles while adding glycerin or glycerin/water mixture
Cap and label jar, and set the jar in a dark location at room temperature. Macerate it for 4–6 weeks, shaking the bottle every day or two to mix. Top off with glycerin as necessary if plant material pokes above the top of the liquid
After 4–6 weeks, decant glycerite into a jar or bowl by pouring through a strainer and squeeze herb material to express every last drop of glycerite.
GLYCERITES

Fig. 1.7: Preparation of glycerites

vative for fresh plant juices, in which half fresh plant juice and half glycerine are mixed, as it keeps the juice green and in suspension better than alcohol. Vegetable glycerin is a clear, odorless liquid produced from vegetable oils such as palm, soy, or coconut oil using high temperature and pressure to split the glycerin molecule from the fatty acids. While sweet, it is not metabolized by the body like sugar. Glycerites are normally less potent than alcoholic extracts and have a shorter shelf life.

Examples: German Chamomile flowers, Echinacea sp, Fennel, Ginger, Hawthorn berry, Elderberry flowers and Lavender.

Oxymels

An oxymel is just a sweet and sour herbal syrup. It contains vinegar, honey and herbs. The word oxymel means acid (oxy) and honey (mel). Oxymels were used to treat a wide, nearly never-ending variety of complaints, from digestion and respiratory diseases to circulation, fevers and sore throats. Oxymels are used as a gargle or as a vehicle for intense herbal aids such as garlic, cayenne, and lobelia.

Cold method: Fill a small jar about half to three-fourths full of herbs. Pour honey over them, then vinegar. Use about one-third of the jar filled with honey to two-thirds of the rest vinegar. Both honey and vinegar act as preservatives, Stir it all together. Just stir or shake it every day for about two weeks, then strain the herbs out, bottle it up and store in a cool place or the refrigerator.

Hot method: Simmer your herbs and vinegar together for ten to twenty minutes. Strain out and stir in honey while the vinegar is still warm. Oxymel is used for sore throats, thick congested coughs or as a general treatment to combat cold and respiratory symptoms. The shelf life for oxymels is about nine months to one year.

Rosemary-Sage Oxymel

- Rosemary sprigs q.s.
- Sage leaves q.s.
- One-third of the jar filled with honey
- Topped off with apple cider vinegar

HERBAL BALMS

These may be classified as ointments meant for massage into the skin for relief of body aches and pains. They normally contain herbal materials which provide a rubefacient effect on the skin and by so doing cause relief of pain. The stability of herbal balms may be compared

to that of herbal ointments since the bases for preparation are similar. The preparation of herbal balms includes four to five parts of oil, one part of beeswax and it is stored in clean sterilized jars.

Marketed Formulation

Arnica St. John's Compound Balm

This floral smelling salve is made with Arnica St. John's herbal oil and calendula flowers into organic olive oil, and combine with beeswax to create a topical salve. It has a calming lavender aroma, and can be applied directly to the skin. Packaged in light weight tins, this salve is easy to take hiking or traveling.

HERBAL TEAS

These are preparations meant for infusion or preparation to be taken as tea. Prepared infusions should be taken immediately after preparation since they do not store well due to the use of water in the extraction process. They normally come as tea bags for hot infusion or as powdered herbal materials (normally pulverized leaves) for boiling in hot water for a few minutes before straining and drinking as tea. Herbal teas are actually mixtures of several ingredients, and are more accurately known as 'tisanes.' Tisanes are made from combinations of dried leaves, seeds, grasses, nuts, barks, fruits, flowers, or other botanical elements that give them their taste and provide the benefits of herbal teas. The stability of the powdered plant material used in the preparation depends on the type and nature of the herbal material as well the moisture content of the powder in the bags and packaging. The shelf life also depends on the extent the herbs have been crushed and storage conditions. Teas stored in airtight containers may last for up to a year while those stored in tea bags may last for a shorter period.

Formulation

Ginseng tea
Ginger tea
Eucalyptus tree

HERBAL PASTES

Pharmaceutically, topical pastes are ointments which may contain as much as 50% powder dispersed in a fatty base. These pastes normally localize the action of irritant or staining materials. They are normally less greasy than ointments. Herbal pastes may contain the herbal ingredient dissolved or dispersed in a base (fatty base if it is meant for topical use or a more aqueous stiff base if it is meant for oral use as is done in herbal toothpaste). Herbal oral pastes should contain only herbal materials that are safe for oral use. The stability of an herbal paste depends on the type of base used as well as the nature of the herbal material incorporated.

Formulations

Long pepper	3 gm
Manchurian wildginger	6 gm
Dried ginger	10 gm

Grind into a powder and mix with a small amount of rice wine, and then paste the mixture on the location of the headache pain. This is for headaches due to internal weakness and present with coldness.

HERBAL OILS

Herbal oils are suspensions or solutions of herbal materials in an oily vehicle. Infused oils are often called macerated oils, and should not be confused with essential oils, which are aromatic oils isolated by distilling the plant material. These preparations are normally meant for external or topical use as liniments. Herbal materials such as leaves with essential oils may normally be found incorporated in these oils. The stability and shelf life of an herbal oil depends largely on the type of oil being used in the extraction process since the stability of various essential oils differs.

Marketed Formulations

Arnica Herbal Oil

Arnica herbal oil contains *Arnica montana* flowers, olive oil and vitamin E oil.

This oil is well-suited for those who physically exert themselves and push their bodies. Absorbs quickly into the skin and fast-acting.

Rosemary Herbal Oil

Rosemary oil has traditionally been a key ingredient in massage oils, and hair care recipes. It contains rosemary oil, organic rosemary leaves, organic olive oil, and vitamin E oil.

HERBAL CREAMS

Creams are semi-solid emulsions of oil and water. They are divided into two types: Oil-in-water (O/W) creams which are composed of small droplets of oil dispersed in a continuous water phase, and water-in-oil (W/O) creams which are composed of small droplets of water dispersed in a continuous oily phase. Oil-in-water creams are more comfortable and cosmetically acceptable as they are less greasy and more easily washed off using water. Herbal creams normally contain the herbal material in either finely sifted form or incorporated as an extract. Creams normally contain antimicrobial preservatives due to the presence of water in the base and may have a relatively shorter shelf life compared to ointments. Herbal creams are those which have a hydrophilic base. If the base is purely hydrophobic, then the preparation must be qualified as an ointment.

Marketed Formulations

Himalaya Herbals Fairness Cream

Earthbound Organics Jojoba and vitamin E cream.

HERBAL SOAPS SHAMPOOS AND BATHS

A soap is a salt of a fatty acid usually made by saponification of a fatty acid with caustic soda or a suitable base. Herbal soaps have the herbal materials incorporated in the detergent base. These herbal materials normally have an antifungal and antibacterial effect on the skin and helps in cleansing of the skin. Herbal soaps are normally meant for microbial skin conditions such as dandruff, eczema, ringworm and boils. Soaps have a relatively longer shelf-life when preservatives or antioxidants are added. Herbal shampoos are cosmetic preparation meant for cleaning hair and scalp for removal of dirt, oils, drandruff and environmental pollutions. Herbal baths are normally prepared by the addition of fresh or dried herbs to bath water. An infusion or tincture of an herbal material may also be added to bath water. Herbs normally used are aromatic in nature and may contain essential oils that may help in relaxation or stress relieve.

Examples

Neem Shampoo

Gram flour	1 kg
Sandal wood powder	250 gm
Neem leaves powder	160 gm
Shikakai powder	1 kg

Orange Shampoo

Methi	250 gm
Shikakai	1 kg
Orange peel	q.s.

MODERN HERBAL FORMULATION

Tablets (Fig. 1.8)

Tablets are unit solid dosage forms containing one or more medicaments intended for oral administration. The mode of administration is swallowing, chewing or by dissolving and dispersing in water before administration. Tablets are usually solid, right circular cylinder, the end surfaces of which are flat or convex and may be available in other shapes—triangular, rectangular, etc.

Herbal tablets are a convenient dosage form and no problems with taste or alcohol are associated with their use. However, tablets contain fixed formulations which cannot be exactly adapted to the needs of the individual patient.

A major potential problem with tablets is the degree of processing required. The minimum processing is required for tablets comprising of powdered herb. Tablets are

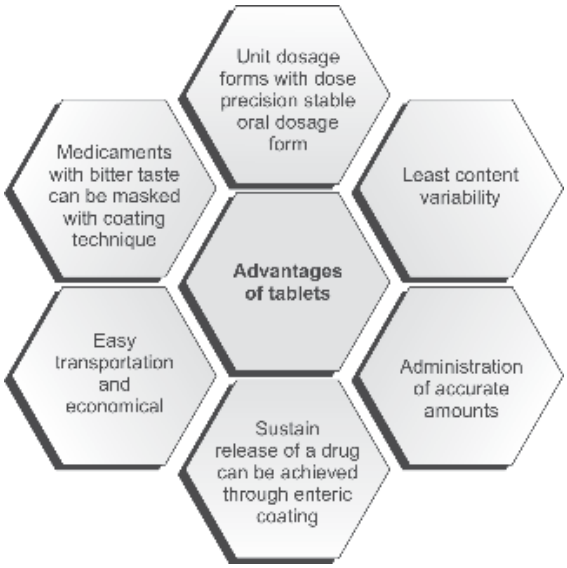

Unit dosage forms with dose precision stable oral dosage form
Medicaments with bitter taste can be masked with coating technique
Least content variability
Advantages of tablets
Easy transportation and economical
Administration of accurate amounts
Sustain release of a drug can be achieved through enteric coating

Fig. 1.8: Advantages of tablets

prepared by extracts. To obtain extracts herbs are mainly extracted with water as a solvent, due to rapid availiabity and low cost of water. The extract obtained is dried using spray drying. Heat liable constituents can be lost during this process also in granulation step in tablet making process. Finally, tablet mixture may be wetted and then dried in oven before final pressing. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets.

Production (Figs 1.9 and 1.10)

Tablets are obtained by compression of uniform volumes of powders or granules by applying high pressures and using punches and dies. The particles to be compressed consist of one or more medicaments, with or without auxiliary substances such as diluents, binders, disintegrating agents, lubricants, glidants, permitted colors and substances capable of modifying the behaviour of the medicaments in the digestive tract. Such substances must be innocuous and therapeutically inert in the quantities present.

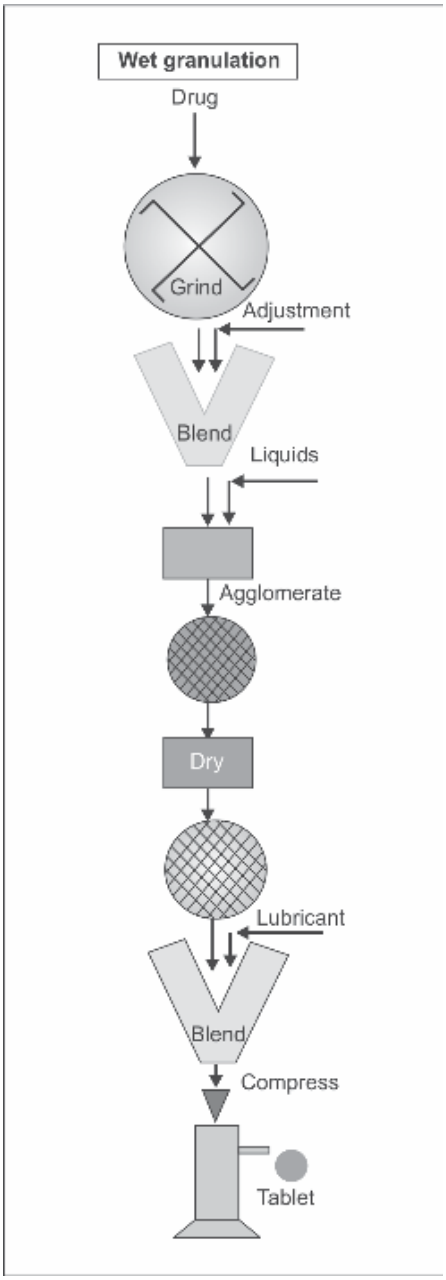


Fig. 1.9: Diagrammatic representation of wet granulation method

In the production of tablets, measures are taken to ensure that they have sufficient strength to avoid crumbling or breaking on handling or subsequent handling. Chewing tablets are manufactured to ensure that they are easily crushed by chewing.

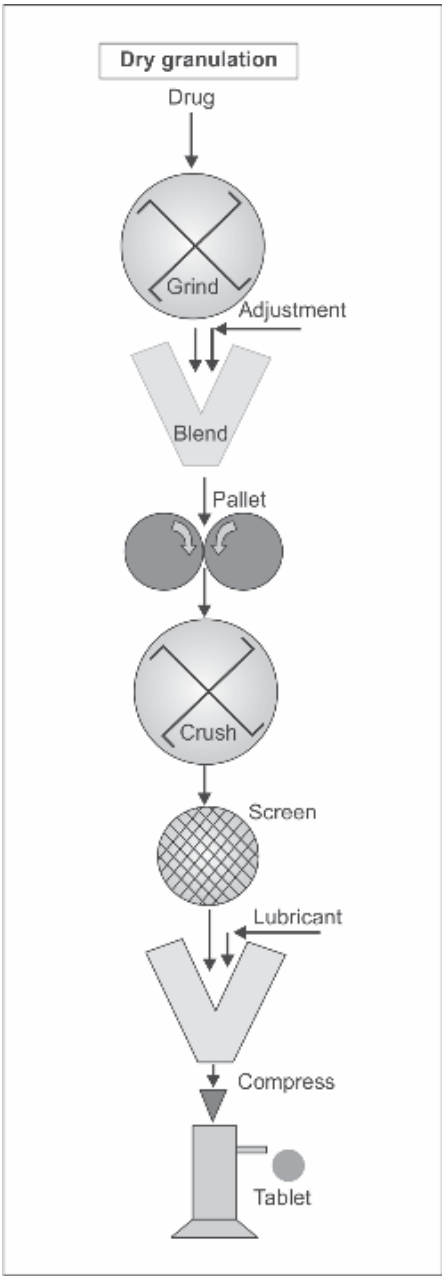


Fig. 1.10: Diagrammatic representation of dry granulation method

During manufacture, packaging, storage and distribution of tablets, suitable means shall be taken to ensure their microbial quality.

Quality control tests for tablet

1. General appearance: Size, shape, odor, taste, texture, legibility, identifying marks
2. Content of active ingredients
3. Uniformity of weight
4. Dissolution
5. Disintegration

Formulation

For bronchitis

Tablet formulation	
Gum tragacanth	180 gm
Wheat starch	180 gm
Glycyrrhiza	180 gm
Kantakari	180 gm
Cucumber	180 gm
Orchid	180 gm

For jaundice

Aloe	150 gm
Agrimonia eupatoria	150 gm
Myrobalan	300 gm
Wild cherry	q.s.

Herbal Capsules

They are solid dosage forms containing drug and fillers encircled in a gelatin. Capsules are available as hard gelatin for dry powdered herbal ingredients or granules, or soft gelatin shells for herbal oils and for herbal ingredients that are dissolved or suspended in oil. The gelatin shell readily ruptures and dissolves following oral administration. The main advantage is that drugs more readily released from capsules compared to tablets, mask the unpleasant taste of its contents and uniformity of dosage can be relatively readily achieved.

Herbal capsules consist of hard shelled gelatin capsules with the plant material finely milled, sifted and filled into shell with appropriate fillers. The stability of herbal capsule preparations is relatively better when compared to aqueous preparations such as decoctions and infusions.

Ointments (Fig 1.11)

Ointments are semisolid preparations that are thicker than creams but thinner than pastes. The ointment formulation consists of active and inactive ingredients added to a base. For herbal formulations, an ointment is made by emulsifying oil phase in water while the mixture is warm, then letting the formulation

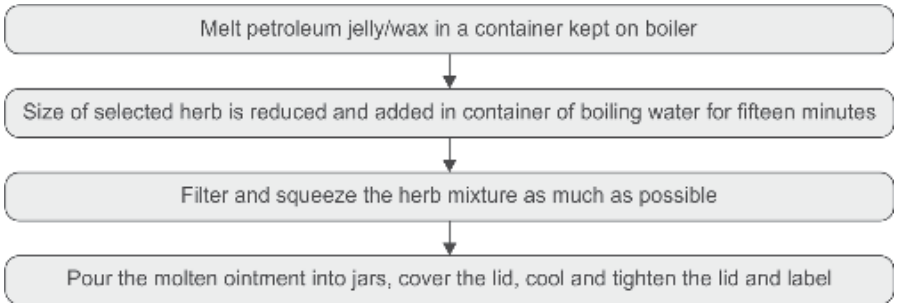

Melt petroleum jelly/wax in a container kept on boiler
Size of selected herb is reduced and added in container of boiling water for fifteen minutes
Filter and squeeze the herb mixture as much as possible
Pour the molten ointment into jars, cover the lid, cool and tighten the lid and label

Fig. 1.11: Preparation of ointments

congeal at room temperature. Herbal drugs are formulated in the form of ointment and are used topically for several purposes, e.g. as protectants, antiseptics, emollients, anti-pruritic, keratolytics and astringents. Ointment bases are always anhydrous and generally contain one or more medicaments in suspension or solution or dispersion.

Ointment bases may be hydrocarbon (oleaginous), absorption, water removable and water soluble type. Ointments may be used as emollients or to apply suspended or dissolved medicaments to the skin. Herbal ointments normally have the plant material either in finely sifted or extracted form incorporated into the base. Ointments are relatively stable when compared with other liquid dosage forms. Storage conditions include to be kept sterilized glass jars with lids for up to three months.

Formulations

Podophyllin ointment

Podophyllum root
Myrrh tincture
Olive oil
Colophony
Beeswax

Percolate the podophyllum root in 95% alcohol for a 1:2 strong tincture. Add the Myrrh tincture, and evaporate both slowly over a low heat. Add the olive oil and rosin, heat until all is dispersed, check for "set" on a metal surface by dripping some on it, and add an beeswax if necessary. Pour into tins, and apply to venereal warts or herpes sores.

Syrup

Syrups are viscous oral liquids that may contain one or more plant drug or plant preparations in solution. To inhibit crystallisation or to modify solubilisation taste and other vehicle properties big quantity of sucrose and sugars added with polyhydric alcohols. Syrups are those formulations which contains ethanol (95%) as a preservative or as a solvent with addition of antimicrobial agents. The advantages of syrup is enlisted in Fig. 1.12.

Note: Sugarless syrups may contain sweetening agents and thickening agents.

Preparation of Syrups

The syrups are manily prepared with three methods that is solution with heating, agitation without heating and percolation. To avoid contamination in the preparation clean equipment is used.

Solution with heating is the quickest method, but not applicable to syrup which contain thermolabile or volatile ingredients. The precautions while using the method are to control temperature to avoid darkening and decomposition of chemical constitutents which is known as caramelization.

The common method of preparation is pouring infusion or decoction of herbs in the pan with sufficient quantity of sugar or honey. Heating is continued till mixture attains syrupy consistency. Cool and pour cooled syrup in sterilized glass container and store in cool dark place as shown in Fig. 1.13.

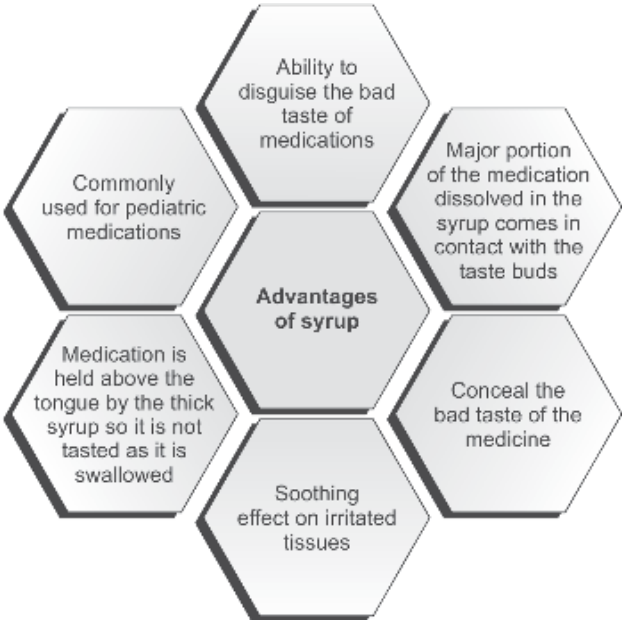

Ability to disguise the bad taste of medications
Commonly used for pediatric medications
Major portion of the medication dissolved in the syrup comes in contact with the taste buds
Advantages of syrup
Medication is held above the tongue by the thick syrup so it is not tasted as it is swallowed
Conceal the bad taste of the medicine
Soothing effect on irritated tissues

Fig. 1.12: Advantages of syrup

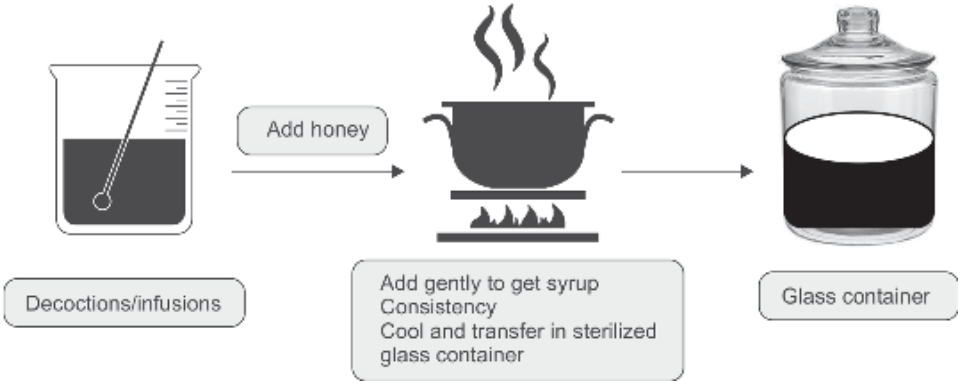


Fig. 1.13: Diagrammatic representation of preparation of syrup

Ingredients: It mainly contains

- Sugars other than sucrose (glucose, fructose), non-sugar polyols (sorbitol, glycerin, propylene glycol, mannitol)
- Other non-nutritive artificial sweeteners (aspartame, saccharin) when a reduction in calories or glucogenic properties is desired, as with the diabetic patient.
- Viscosity adjusters such as methylcellulose are added to impart the characteristic viscosity of syrups.
- Cosolvents and preservatives such as polyols provide favourable viscosity, reducing cap-locking.
- A 70% sorbitol solution is available as a vehicle.

Quality control tests for syrups

1. Visual inspection/physical appearance
2. Light transmission matter/color
3. pH measurement
4. Physical stability in syrups
5. Sucrose concentration

6. Weight per ml
7. Viscosity
8. Optical rotation
9. Solubility
10. Assay of active ingredients

Examples

1. **Glycerrhiza syrup** has been recommended for disguising the salty taste of bromides, iodides, and chlorides. This has been attributed to its colloidal character and its double sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing B complex vitamins.
2. **Acacia syrup** because of its colloidal character is of great value as a particular vehicle for masking disagreeable taste of many medicaments.
3. **Raspberry syrup BP** is one of the most efficient flavoring agents, and is especially useful in masking the taste of bitter drugs.
4. **Wild cherry bark syrup:** Simple syrup can be used as the solvent in which to macerate herbs, rather in the same fashion as making a tincture. This is particularly recommended for wild cherry bark, *Prunus serotina*, as the therapeutic hydrocyanates that develop on exposure to water are not stable to heat. Use about 200 g of fresh or dried cherry bark per litre of simple syrup, leaving to macerate for 3–4 weeks before straining and bottling.
5. **Thyme and liquorice syrup:** There are dozens of different recipes for this popular syrup, a great standby for coughs caused by seasonal infections.

Glycyrrhiza glabra, cut	75 gm
Thymus vulgaris	100 gm
Water	1.5 litres
Sugar	1.8 kg

6. **Barberry syrup:** Place the barberry bark in sufficient water to cover well, bring to the boil and simmer gently for 1–2 hours, topping up the water if necessary. Remove from the heat, press and filter when cool enough to handle. Return the decoction to the heat, simmering again until it has reduced to 500 ml. (If you have reduced it too much, which can easily happen, top it up to 500 ml with plain water.) Add the sugar, bring it back to simmering point whilst stirring until the sugar is completely dissolved, remove from heat and bottle when cool.

Berberis vulgaris	200 gm
Water, approx	1.5 litres
Sugar	800 gm

Herbal Suppositories

Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert localized or systemic effects. They are prepared by moulding with the incorporation of the medicinal agent into a suitable base which should melt or dissolve at body temperature to exert the therapeutic effect. Suppositories may be used for local or systemic effects. Herbal suppositories are normally prepared by mixing powdered and finely sited herbs or extracts with cocoa butter as the base. They are normally used to soothe inflamed surfaces of the nasal mucosa and aid the healing process; reduce swollen membranes and overcome pus filled discharge or to act as a laxative to treat constipation. The stability of suppositories depends on the temperature of storage and packaging. They are relatively stable at low temperatures of storage.

Herbal Pessaries

Pessaries are similar to suppositories but are meant for insertion into the vagina for local or systemic effects. Herbal pessaries may also be made using a glycerated-gelatin base which dissolves at body temperature to release herbal ingredients for the desired local or systemic effects. The stability of pessaries may be compared to that of suppositories.

Formulations

Cervical dysplasia suppositories

Echinacea fluid extract	30 ml
Calendula tincture	10 ml

Glycerin	175 ml
Gelatin (pharmaceutical grade)	25 gm

Fill a plastic roll of disposable 3 or 5 ml suppository molds up to the top of the form line.

A suppository should be inserted at night into the vagina and as close to the cervix as practical. Gelatin-based suppositories do not melt like those made with cocoa butter or gelatin, but dissolve slowly over 8–12 hours, maintaining the herb presence for long enough to facilitate resolution and stimulate regeneration of the tissues.

HPV (venereal wart) suppositories

Echinacea fluid extract	30 ml
Glycerin	175 ml
Gelatin (NF)	25 gram
Thuja oil	5 ml

Thuja oil to the dissolved syrup just before you begin to pour into the molds. Each suppository ends up containing about a drop of Thuja oil very easily tolerated.

Herbal Poultices and Plasters

Poultices are made by mashing fresh herbs, wrapping in a gauze and applied to an affected area of the skin after the temperature is suitable for application. Poultices may be used externally to relax muscles or to ease minor skin eruptions, poison ivy, insect bites, superficial wounds, and inflammation. Since they are normally made from fresh herbs, they should be used immediately and cannot be stored.

Herbal Compresses and Fomentations

Compresses are normally prepared from an infusion or tincture in hot or cold water by soaking a cotton cloth or gauze. Compresses may be used externally and can be either warm or cold. Cold compresses reduce inflammation and help to relieve pain. They are usually used in the treatment of sprains, contusions, strains, inflammation, headaches, and insect bites. Warm compresses are used to increase circulation to an area and to allow muscles, tendons, and ligaments to stretch.

Herbal Liniments

Liniment is a medicated topical preparation for application to the skin. Sometimes called balms or heat rubs, liniments are of a similar or greater than lotions and are rubbed in to create friction, unlike lotions, ointments or creams but patches, sticks and sprays. Liniments are for external use for aches and pains and are normally used as warming massage mediums to relieve soreness in muscles and ligaments. Heat-inducing herbs such as cayenne are normally used in the preparation of liniments together with alcohol for extraction or a mixture of alcohol and/or oil. Liniments should not be used on cuts or broken skin. The stability of liniments is similar to that of herbal oils.

Rotgut Liniment

Tobacco
Baneberry root
Datura leaves
Ginger root
Rubbing alcohol (70% isopropyl)

Grind up the herbs together and soak them in the rubbing alcohol (shaking daily) for two weeks. Apply the squeezed-out liniment by hand or with a liniment moistened cloth to sprains, bruises and hyperextensions. Wash your hands immediately.

Lozenges

Lozenges are solid preparations that contain one or more medicaments, usually in a flavored, sweetened base, that are intended to dissolve or disintegrate slowly in the mouth. They can be prepared by molding (gelatin and/or fused sucrose and sorbitol base) or by compression of sugar-based tablets. Molded lozenges are sometimes referred to as pastilles, whereas compressed lozenges may be referred to as troches. Lozenges may be prepared by the use of the powdered herbs together with excipients such as sugar and honey to provide the sweet taste, gums (acacia and tragacanth) and the white of an egg in some instances. The

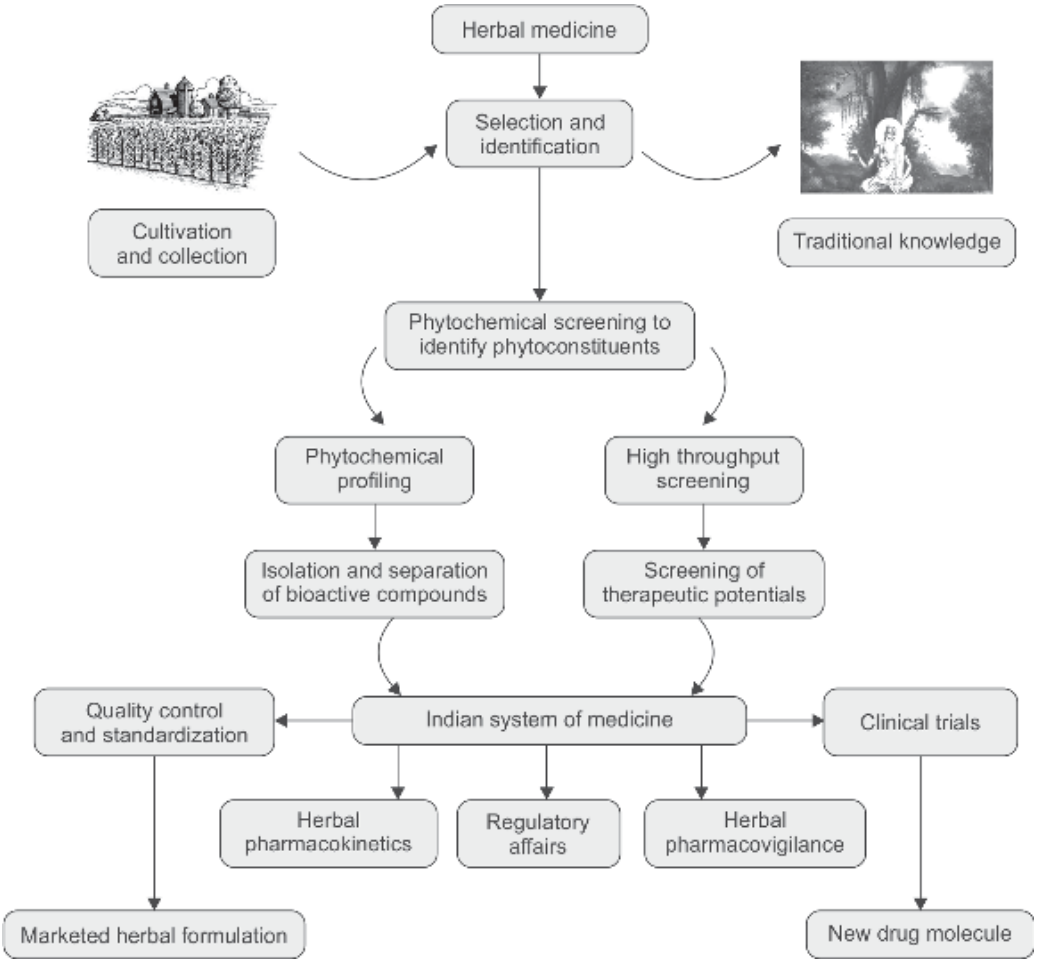


Fig. 1.14: Leveraging approaches for the development of herbal medicine

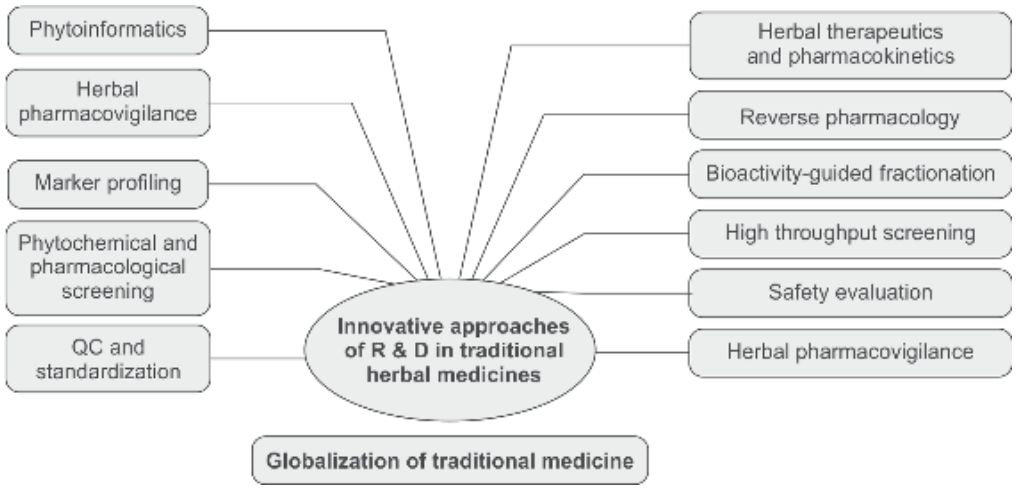


Fig. 1.15: Innovative approaches of R & D in traditional herbal medicines

Cure disease by targeting
Cure diseases by transporting the drug to affected area
Delivering the herbal drug at predetermined rate
Advantages of novel herbal drug carriers
Increases bioavailability
Delivery of drug at the site of action
Reduce toxic effects

Fig. 1.16: Advantages of novel herbal drug carriers

lozenges normally may be used to sooth soreness in the throat as well as help in the treatment of throat infections. Lozenges normally do not contain disintegrating agents. The shelf life of lozenges may be compared to that of tablets but should be determined using an appropriate stability protocol.

Patent Formulation of Ginseng Lozenges

Ginseng
St John's wort
Passion flower
Water
Sugar/syrup
Corn syrup
Pippermint oil

HERBAL NOVEL DRUG DELIVERY SYSTEM

Herbal medicines have gained worldwide appreciation due to their therapeutic potency and fewer adverse effects as compared to the synthetic ones. Novel drug delivery is modified herbal drug delivery which growths the therapeutic value as well as reducing toxicity. The carriers of herbal drug in novel drug delivery system tragets the affected area of human body and transportation of drug to that area. The system is advantageous in transporting predetermined rate of the herbal drug with minimum toxic effects and increased bioavailability. It is used to achieve modified delivery of herbal drugs, increased therapeutic value as well as reducing toxicity as shown in Fig. 1.16.

Incorporation of drugs in the novel delivery systems helps in

- Increased solubility
- Enhanced stability
- Protection from toxicity
- Enhanced pharmacological activity
- Improved tissue macrophage distribution
- Sustained delivery
- Targeted delivery
- Enhanced bioavailability
- Protection from physical and chemical degradation.

The novel carriers for drug delivery are enlisted in Fig. 1.17.

PHYTOSOMES (Fig. 1.18)

It is an advanced form of herbal products with the property of better absortion, utilization and better activity as compared to conventional

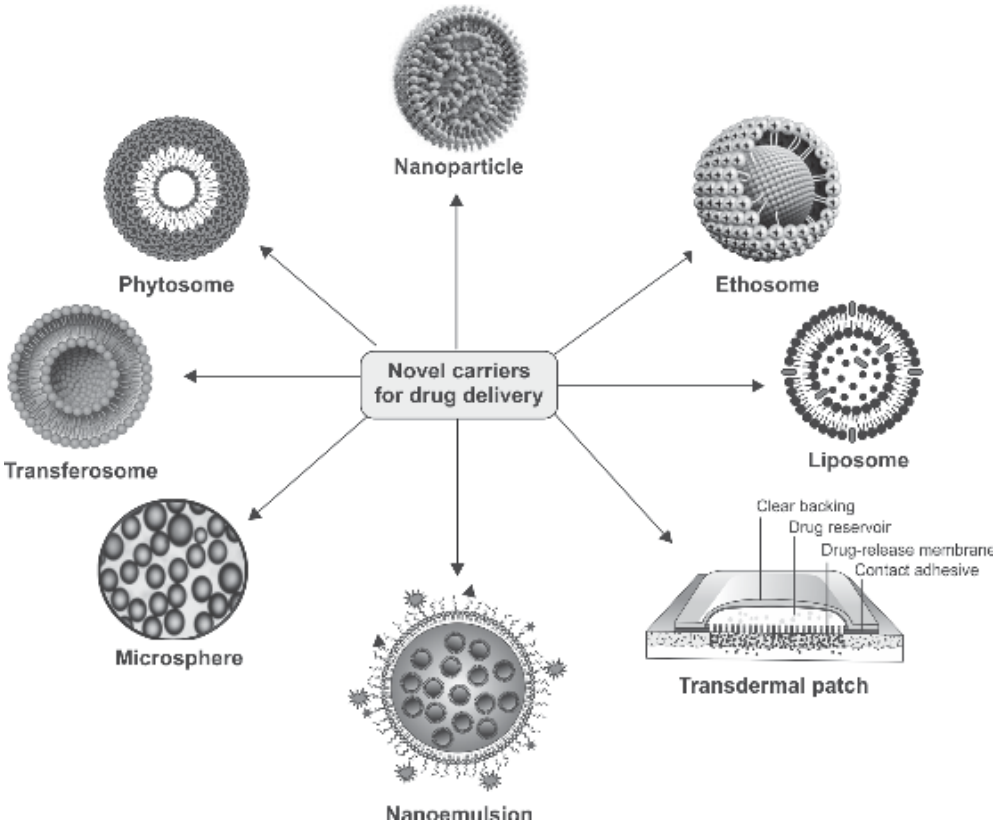


Fig. 1.17: Novel carriers for drug delivery

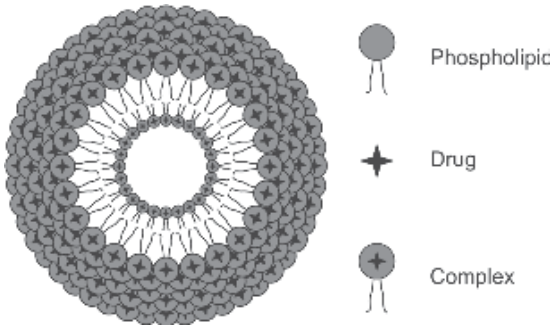


Fig. 1.18: Phytosomes

herbal extracts. The chief components of phytosome are bound to phosphatidylcholine—an emulsifying compound derived from soy. The other bioactive constituents are flavonoids (e.g. anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle).

But flavanoids are poorly absorbed due to two factors as they are multiple-ring molecules too large to be absorbed by simple diffusion, while they are not absorbed actively. Second having poor miscibility with oils and other lipids, severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. PC, the principal molecular building block of cell membranes, is miscible both in water and in oil/ lipid environments, and is well absorbed when taken by mouth. Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis. Phytosomes are not

Table 1.1: Phytosomal herbal products

Phytosomes	Source	Use
Silybin	Silybin flavonoids from *Silybum marianum*	Hepatoprotective, antioxidant for liver
Ginseng	Ginsenosides from *Panax ginseng*	Nutraceutical and immunomodulator
Green tea	Epigallocatechin from *Thea sinensis*	Anti-cancer, nutraceutical
Grape seed	Procyanidins from *Vitis vinifera*	Nutraceutical, systemic antioxidant, cardio-protective.

liposomes; structurally, the two are distinctly different. The phytosome is a unit of several molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose active phytomolecules, but without specifically bonding to them.

Properties of Phytosomes

Physico-chemical Properties

1. Phytosomes are prepared by reaction of stoichiometric amount of phospholipid with the standardized plant extract as substrate. The substrate interaction is due to the formation of hydrogen bond between the polar head (i.e. phosphate and ammonium group) and the polar functionalities of the substrate.
2. The size of phytosome varies from 50 nm to a few hundred μm.
3. Phytosomes treated with water assume a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals these liposomal structures acquired by phytosomes.
4. Regarding the solubility of phytosomes, the complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. But the phytosomes of certain lipophilic phytoconstituents like curcumin has shown increased water solubility upon complexation with phospholipids.

Biological Properties

1. Phytosomes are novel complexes which are better absorbed and utilized, hence they produce more bioavailability and better result than the conventional herbal extract or non-complexed extracts, which has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.
2. Phytosomes express their behaviour in physical or biological system because of their physical size, membrane permeability, percentage entrapment, chemical composition, quantity and purity of the materials used. The phytosomes should not be confused with liposomes where hydrophilic drug molecules are entrapped within a cavity or spaces between the membranes. The liposomes may involve several hundred phospholipid molecules for this entrapment and are usually now being used for cosmetic purposes. Instead, the phytosomes involve interaction of 1–4 phospholipid molecules with the phytoconstituents which are chemically anchored to each other. Several researches have shown the phytosomes to be a better alternative for liposomes in terms of membrane permeability and stability.

HERBAL CONSTITUENTS USED IN PHYTOSOMAL DRUG DELIVERY

Flavonoids

Flavonoids are broader class of dietary antioxidants called polyphenols widely distributed in food and medicinal plants. They are found abundant in berries, some fruits, a few vegetables and tea beverages. Flavonoids are used as antioxidant, anti-inflammatory, anti-allergic, antiviral, anticancer, immune-stimulant applications.

Table 1.2: Marketed products of phytosomes

S. No.	Marketed preparation	Properties
1.	**Leucoselect** (Oligomeric polyphenols (grape procyanidins) complexed with soy phospholipids)	• Improved oral bioavailability of procyanidins. • To exert a protective activity on the cardio-vascular system. • Unique antioxidant effect.
2.	**Ginkgoselect** (Easy absorbable form of the standardized extract of *Ginkgo biloba* leaves)	• Its better oral bioavailability and the good tolerability make it the ideal product even for long-term treatments. • It also can ameliorate reduced cerebral circulation.
3.	**Greenselect** (Contains a totally standardized polyphenolic fraction (not less than 66.5%) obtained from green tea leaves)	• The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. • Potent modulators of several biochemical processes.
4.	**Siliphos** (Most absorbable form of silybin).	• Prevents liver damage of different etiology. • To be effective as antihepatotoxic.
5.	**Mirtoselect** (An extract of bilberry which provides anthocyanosides).	• These improve capillary tone, reduce abnormal blood vessel permeability, and are potent antioxidants • They hold great potential for the management of retinal blood vessel problems and venous insufficiency.
6.	**Sabalselect** (Extract prepared from saw palmetto berries)	• It delivers fatty acids, alcohols and sterols that benefit prostate health. • May benefit non-cancerous prostate enlargement.
7.	**Lymphaselect** (Standardized extract from *Melilotus officinalis*)	• It is indicated for venous disorders, including chronic venous insufficiency of the lower limbs.
8.	**Oleaselect** (Preparation from olive oil polyphenols)	• These are potent free radical scavengers (anti-oxidants), inhibit harmful oxidation of LDL cholesterol. It also has anti-inflammatory activity.
9.	**Polinacea** (Immunomodulating preparation made from *Echinacea angustifolia*)	• It enhances immune function in response to a toxic challenge. • It enables cost-effective delivery and synergistic benefits from the phospholipid nutraceuticals intrinsic to life.

Terpenoids

Natural products and related compounds formally derived from isoprene units. They contain oxygen in various functional groups. This class is subdivided according to the number of carbon atoms as *terpenes*. The skeleton of terpenoid may differ from strict additivity of isoprene units by the loss or shift of a fragment, generally a methyl group.

Carotenoids

Carotenoids are among the most widely distributed pigments and naturally exhibit red, orange and yellow colors.

Carotenoids are lipid-soluble pigments, which can be found in many kinds of fruit, vegetables, fungi, flowers and some kinds of animals.

Isoprenoids

It includes both *hydrocarbon* and oxygenated derivatives derived from isoprene (2-methyl-buta-1,3-diene). The skeleton of isoprenoids may differ from strict additivity of isoprene units by loss or shift of a fragment, commonly a methyl group.

Terpenes

Hydrocarbons of biological origin having carbon skeletons formally derived from isoprene. It is subdivided as C5 hemiterpenes, C10 monoterpenes, C15 sesquiterpenes, C20 diterpenes, C25 sesterterpenes, C30 triterpenes, C40 tetraterpenes (carotenoids), and C5n polyterpenes.

Phosphatidylcholine

Phosphatidylcholine is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes, and the molecular properties that suit PC for this role, also render it close to ideal for its phytosome role.

LIPOSOMES

Liposomes are biodegradeable, colloidal and spherical vesicles (0.05–5.0 m in diameter) composed of a bilayer membrane entrapping an aqueous core. Liposomal-based drug delivery is advantageous specifically in enhancing the therapeutic index, either by increasing the drug concentration in the tumour cells and by decreasing the exposure to normal cells. Liposomes have been used to change the pharmacokinetic profile of various drugs, herbs, enzymes, etc., as shown in Fig. 1.19.

Microspheres

Microspheres are spherical particles consisting of size ideally 1–300 m. Each particle is matrix of the drug dispersed in the polymer and drug is released as a first-order process. The polymers used for the fabrication of the microspheres are biodegradable or non-biodegradable. Various polymers have been used for fabrication of these microparticulate carriers such as albumin, gelatin, modified starch, polypropylene, dextran, polylactic acid and polylactide-co-glycolide, etc. (Fig. 1.20).

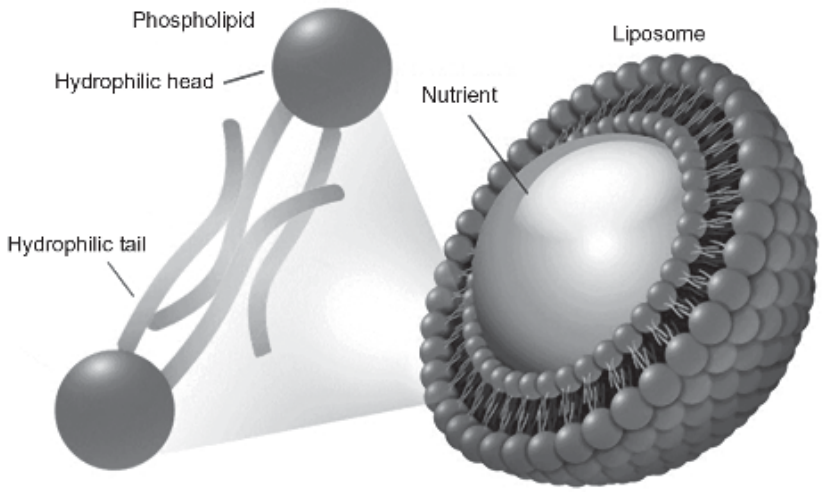


Fig. 1.19: Liposomes

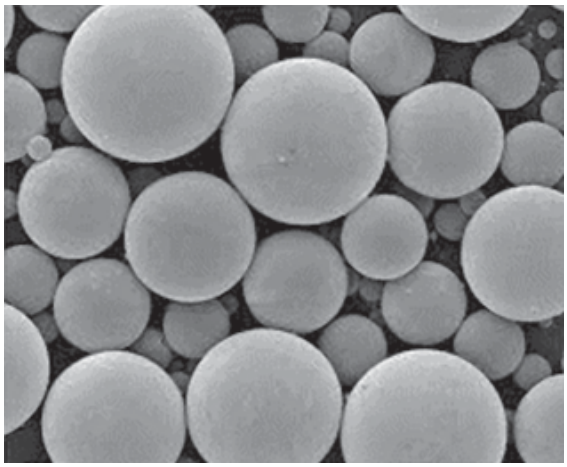


Fig. 1.20: Microsphere

Nanoparticles (Fig. 1.21)

Nanoparticles are the submicron size particles having size range of 10 to 1000 nm. The main advantages of the nanoparticles are their stability and long-term storage. The particle size and surface characteristics of nanoparticles can be easily modified for controlled and targeted drug delivery. Nanosizing leads to increased solubility of components and reduction in the dose via improved absorption of active ingredient. Nanoparticles are efficient delivery systems for the delivery of both hydrophilic and hydrophobic drugs.

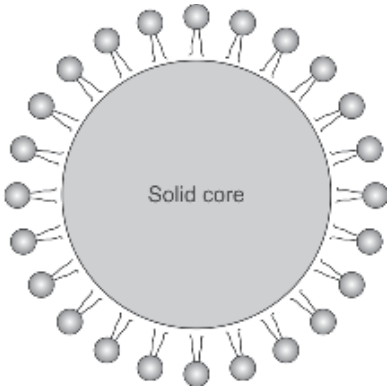


Fig. 1.21: Nanoparticles

TRANSFEROSOMES (Fig. 1.22)

Transferosomes are phospholipid vesicles which act as potential carriers for the transdermal delivery of the drug. They overcome the difficulty of penetration through the *stratum corneum* and can easily penetrate through the intracellular pores of the skin due to their flexibility. Transferosomes are

Table 1.3: Liposomal herbal formulations

Bioactive component/plant	Application
Essential oil from *Atractylodes macrocephala* Koidz	Increase in solubility and bioavailability
Essential oil of *Origanum dictamnus*	Increase in activity
Quercetin	Increase in bioavailability and reduction in side effects
Silymarin extract	Increase in hepatoprotective activity
Capsaicin	Increase in permeation as prolongation of action
Taxanes	Decrease in toxicity

Table 1.4: Microsphere herbal formulations

Name of bioactive component/plant	Application
Silymarin	Sustained release
Zedoary turmeric oil (microencapsulation techniques)	Increase in bioavailability as well sustained release occurs
Rutin	Specific delivery to cardiovascular and cerebrovascular region
Camptothecin (spray dry process)	Significant decrease in dose by enhancing the solubility

Table 1.5: Nanoparticle containing herbal drugs

Name of bioactive component/plant	Application
Paclitaxel (controlled nanosystem)	Reduction in side effects
Curcumin (poor aqueous solubility)	Increase in solubility/potential carrier for the treatment of cancer
Triptolide	Increase in solubility
Quercetin	Increased drug release and antioxidant effect (approx 74 times)
Taxol (emulsion solvent evaporation technique)	Sustained release/enhanced bioavailability
Paclitaxel and doxorubicin (using Brij 78 surfactant, P-glycoprotein mediated drug)	Inhibition of resistance and thus increases anticancer activity
Cuscata chinensis (flavonoid/lignan)	Nanosuspension reduced the dose 5 times compared to alcoholic extract

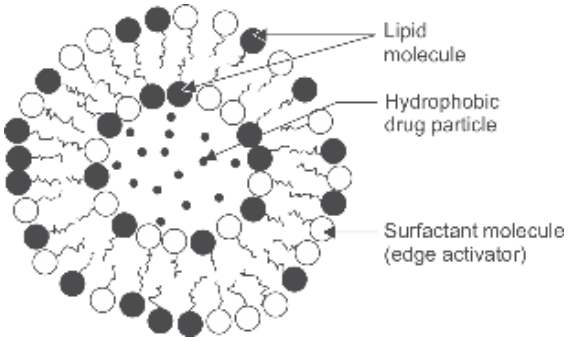


Fig.1.22: Herbal transferosomes

fabricated by using phospholipids (act as vesicle forming material), surfactant (providing flexibility), alcohol (solvent) and buffering agent (as hydrating medium).

ETHOSOMES

Ethosomes are vesicles composed of phospholipids and high concentration of ethanol as shown in Fig. 1.23. High concentration of ethanol in the vesicles leads to enhancement in their permeability through the skin by fluidizing the lipid domain of the skin.

Table 1.6: Herbal transferosomes

Name of bioactive component/plant	Application
Capsaicin transferosomes	Increased skin penetration
Curcumin transferosomes	Increased skin penetration (potent anti-inflammatory)
Vincristine sulphate transferosomes (prepared with lecithin and sodium deoxycholate)	Increase in permeability
Colchicine transferosomes (by shaking method)	Reduction in GIT side effects

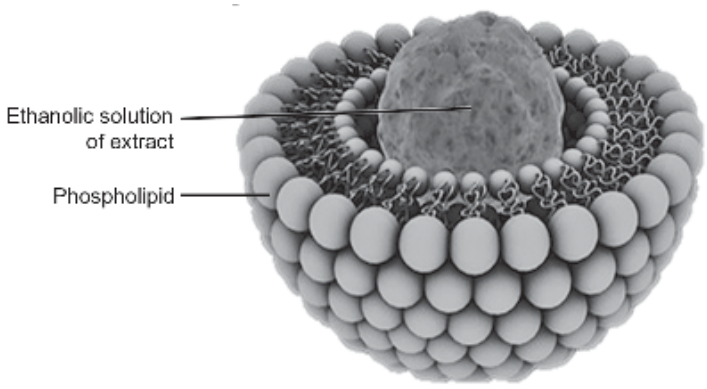


Fig. 1.23: Herbal ethosomes

Table 1.7: Herbal ethosomes

Name of bioactive component/plant	Application
Ethosomal suspension of ammonium glycyrrhizinate	Increased drug permeation through dermis for inflammatory disorders
Triptolide	Increase in bioavailability
Sophora alopencerides (ethosomes prepared by using isolated alkaloids)	Increase in permeability and useful for topical delivery of alkaloids

Ethosomes have been reported for transdermal delivery of the hydrophilic and impermeable drugs such as minoxidil, testosterone, bacitracin and cannabidol. Efficient carrier for topical/ transdermal route. Used for both hydrophillic and hydrophobic drug.

NANOEMULSIONS/MICROEMULSIONS (Fig. 1.24)

Nanoemulsions and microemulsions are the emulsions of O/W type having the size range of several microns. They are prepared by using the surfactants which are considered safe for the human use and approved by the FDA. These types of emulsions have higher surface area and hence can easily penetrate through the skin. They are also non-toxic and non-irritant in nature and can be used in the animals and veterinary purpose.

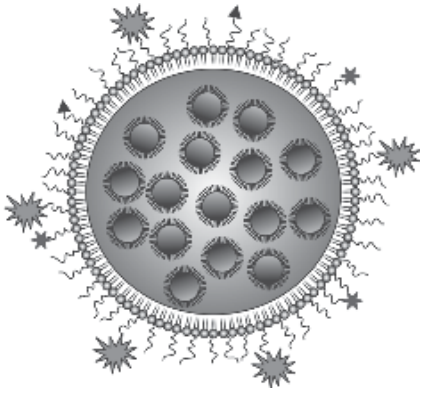


Fig. 1.24: Nanoemulsions and microemulsion herbal formulations

TRANSDERMAL SYSTEMS (Fig. 1.25)

Transdermal drug delivery devices are the polymeric formulations which are applied over the skin and deliver the drug at predetermined rate and for predetermined time. There are various types of the transdermal delivery devices which can be formulated by using the polymer matrix, adhesive bandage and permeation enhancers. Transdermal delivery system provides the advantage of controlled drug delivery, enhanced bioavailability, reduction in side effects and easy application. Transdermal drug delivery systems are potentially used for the

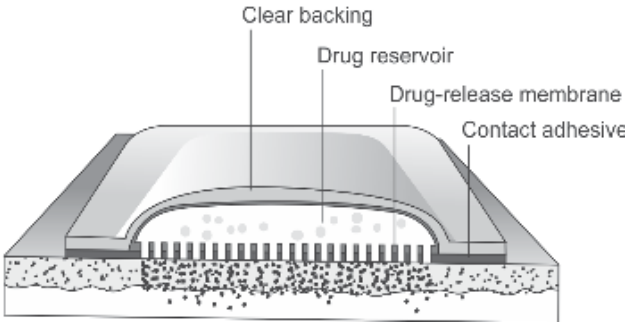


Fig. 1.25: Transdermal system

Table 1.8: Nanoemulsions and microemulsion herbal formulations

Name of the bioactive component	Target site/ biological activity
Norcantharidin microemulsion	Liver
Puerarin microemulsion	Cardiovascular and cerebrovascular disease
Silybin nanoemulsion	Liver
Berberine nanoemulsion	Tumor
Matrine nanoemulsion	Anti-bacterial, anti-inflammatory, anti-virus

Table 1.9: Assessment of the drug carrier

Characters	Liposomes	Transferosome	Ethosomes	Microsphere	Nanoparticles	Phytosomes	Nanoemulsions/ microemulsion
Size	0.05–5.0 Mm	0.05–10.0 Mm	0.05–10.0 Mm	1–300 µm	10 to 1000 nm	0.05–5.0 µm	0.01 to 50 µm
Composition	Phospholipids and cholesterol	Phospholipids surfactant	Phospholipids ethanol	Polymers	Polymers	Phospholipids and cholesterol surfactant	Oil phase and aqueous phase
Flexibility	Rigid in nature	High deformability due to surfactant	High deformability and elasticity due to ethanol	Rigid and hard in nature, bigger in size	Small and rigid with hard nature	Similar to liposomes	High deformability (globules)
Mechanism	Diffusion/ fusion/ lipolysis	Deformation of vesicle	Lipid perturbation	Diffusion/ erosion	Diffusion/ erosion	Diffusion/ fusion/ lipolysis	Diffusion/fusion/ deformation of globules
Route of administration	Oral, topical, transdermal and parenteral	Topical and transdermal	Topical and transdermal	Oral, topical, transdermal and parenteral	Oral, topical, transdermal and parenterals	Oral, topical and transdermal	Oral, topical, transdermal and parenteral
Marketed product	VincaXome Vincristine Solid tumors NeXstar, USA				Abraxane Paclitaxel Abraix Bioscience Cancer treatment AstraZeneca USA	Meriva-SR curcumin anti-inflammatory, detoxification, cardiovascular Thorne Research USA	

sustained delivery of the drugs up to several days or even months.

IMPLANTS

These are the polymeric devices which are used for the controlled and sustained delivery of the drugs. These are directly placed in the body fluids/cavities and are fabricated by using biodegradable polymers. A micro-surgery is always required for the insertion of these devices. Implants of the extract of Danshen (*Radix Salviae Miltiorrhizae)* have been developed using chitosan and gelatin. This drug is used for healing of muscles and tissues in abdominal cavities (Fig. 1.26).

MICROPELLETS

These are the solid particles which fall in the range of 1–1000 m. Controlled release pellets are used for the delivery of drugs to specific sites and for the extended period of time. Used for the delivery of two incompatible drugs simultaneously at same or different sites. It prevents dose dumping which occurs with the conventional dosage forms, i.e. vomiting, loss of appetite and nausea.

Pellets are also used for the coating and taste masking of the formulations. Pectin-hydroxy-propyl methylcellulose (HPMC) coated curcumin pellets were prepared for delivery of the curcumin in the colon to treat the inflammatory disease. Andrographolide (*Andrographis paniculata wall)* micropellets can be prepared by sodium alginate to release the drug away from the upper part of GIT and prevent the GIT irritation problems (Fig. 1.27).

COMPLEXATION

Complexation is the association between the two or more molecules to form a nonbonded entity with a well-defined stochiometry. Various complexing agents such as EDTA, cyclodextrins and polymers have been used for the complexation. Curcumin is a poorly soluble drug; its solubility has been increased by formation of curcumin soya lecithin complex for hepatoprotective activity. Complexation increase permeability of the curcumin.

CONCLUSION

Medicinal herbs as potential source of therapeutics aids have attained a significant

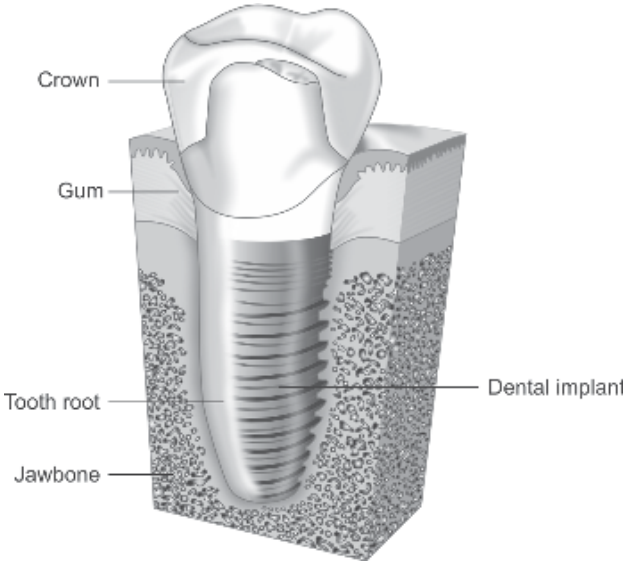
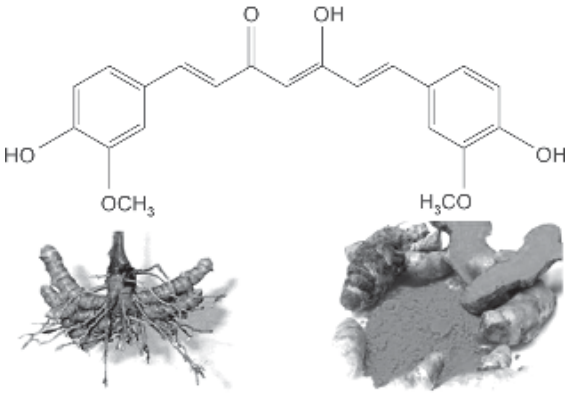


Fig. 1.26: Implants

Fig. 1.27: Micropellets



role in health system all over the world for both humans and animals not only in the diseased condition but also as potential material for maintaining proper health. Herbs are staging a comeback, herbal 'renaissance' is happening all over the globe and more and more people are taking note of herbal therapies to treat various kinds of ailments in place of mainstream medicine. Modern medicine is failing to effectively treat many of the most common health conditions, many natural measures are being shown to produce better results than drugs or surgery without the side effects.

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Modern medicine cures a particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Drug delivery system is the method by which an optimum amount of the concerned drug is administered to the patient in such a way that it reaches exactly the 'site of action' and starts working then and there. Novel drug delivery system attempts to eliminate all the disadvantages associated with conventional drug delivery systems.

CHAPTER 2

Formulation Consideration of Herbal Dosage Forms

DOSAGE FORMS OF HERBAL MEDICINAL PRODUCTS

Over the last three decades, there has been a huge increase in use of herbal products across the world. About 80% of the world's population, especially those in developing countries, uses herbal medicines as part of their primary health care needs. Dosage forms are the means by which plant parts or constituents are distributed within the body to different sites of action. Classification of finished herbal products into dosage forms will aid to outline specific protocols for quality control and stability testing (Fig. 2.1).

Herbal formulations are defined as finished, labelled medicinal products that contain active ingredients aerial or underground parts of plants or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Herbal medicines may contain excipients in addition to the active ingredients. Finished herbal products or herbal drug preparations are varied and various solvents may be used for their extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates (Fig. 2.2).

The demand of herbal medicinal products is increasing which resulted in the more production of products. If the production is increased it may lead to longer storage which may lead to deterioration of products, thereby compromise product quality with adverse consequences on patient safety. So it is

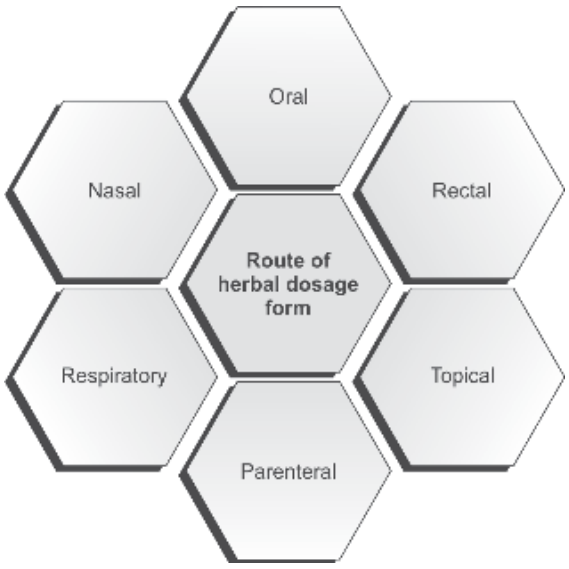


Fig. 2.1: Route of herbal dosage forms

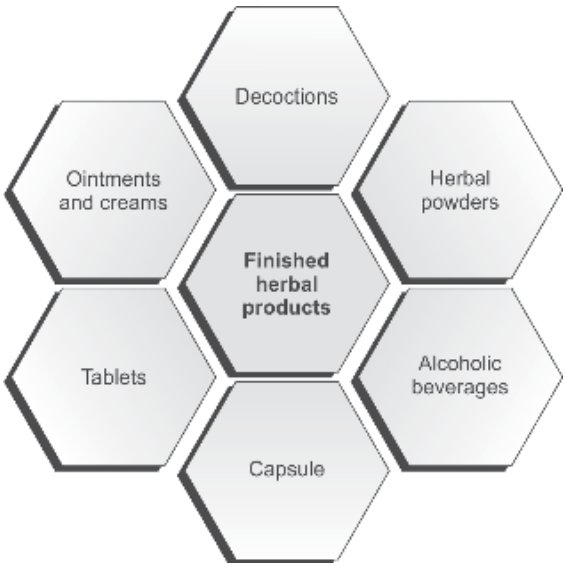


Fig. 2.2: Various dosage forms of finished herbal products

necessary to enhance product quality by determining its shelf life during storage and usage using appropriate guidelines. Stability studies may involve physical or sensory tests, microbiological tests and chemical or chromatographic/spectral tests.

Drug substances are seldom administered alone rather they are given as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical functions. Selective use of these non-medicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types.

The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, avor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to prescribe.

HERBAL EXCIPIENTS

Excipients were defined as the substance used as a medium for giving a medicament, that is to say with simply the functions of an inert support of the active principle or principles.

Pharmaceutical excipients (Fig. 2.3) can be defined as non-active ingredients that are mixed with therapeutically active compound(s) to form medicines. The ingredient which is not an active compound is regarded as an excipient. Excipients affect the behavior and effectiveness of the drug product more and more functionality and significantly.

Excipients are also derived from natural sources, synthesized chemically, or prepared semi-synthetically starting from natural sourced materials. They range from simple, usually well-characterized, organic or inorganic molecules to highly complex materials that are difficult to fully characterize.

Fig. 2.3: Pharmaceutical excipients of plant origin

The specific application of natural polysaccharide polymers in pharmaceutical formulations include to aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. These natural excipients find applications in the pharmaceutical industry as binding agents, disintegrates, sustaining agents, protectives, colloids, thickening agents, gelling agents, bases in suppositories, stabilizers, and coating materials. The advantages of natural plant-based excipients include that they are of low cost, natural origin, fairly free from side effects, biocompatible, and bio-acceptable, with a renewable source, environmental-friendly processing, local availability, better patient tolerance, as well as public acceptance.

CLASSIFICATION OF HERBAL EXCIPIENTS
(Figs 2.4 and 2.5)

Classification of excipients is based on their role in the pharmaceutical formulation, their interactions influencing drug delivery, or their chemical and physicochemical properties.

Fig. 2.4: Classification of excipients

Fig. 2.5: Significance of herbal excipients

Table 2.1: Classification of natural excipients according to source of their origin

Animal	Vegetable	Mineral
Shellac	Agar	Paraffin
Honey	Guar gum	Kieselguhr
Lactose	Turmeric	Talc
Spermaciti	Vanilla	Asbestos
Lanolin	Saffron	Calamine
Gelatin	Pectin	Chalk
Beeswax	Starch	Shilajit
Cochineal	Kokum butter	Kaolin

Table 2.2: Classification of natural excipients according to their pharmacological action

S. no.	Type	Examples
1.	Antioxidant	Tocopherol, vitamin C, citric acid, lecithin
2.	Antibacterial	Neem, curcuma
3.	Adsorbents	Kaolin, pectin, magnesium oxide
4.	Antiadherants	Talc, magnesium sterate, corn starch
5.	Binding agents	Acacia, tragacanth, gelatin
6.	Colourant	Amarnath, caramel, chlorophyll
7.	Disintegrating agents	CMC, starch
8.	Diluents	Starch, sucrose, lactose, mannitol
9.	Emulsifying agents	Guar gum, agar and acacia
10.	Flavors	Vanilla, lemon oil, orange oil
11.	Glidants	Aerosil, talc
12.	Lubricants	Stearic acid, cocoa butter
13.	Sweetening agent	Honey, glycyrrhiza
14.	Thickening agent	Methyl cellulose, tragacanth

Table 2.3: Classification of natural excipients according to their chemical nature

S. no.	Chemical nature	Example
1.	Carbohydrates	Acacia, tragacanth, agar, honey, pectin, guar gum, dextrin
2.	Fixed oils	Cod liver oil, castor oil, soybean oil, almond oil
3.	Fats and waxes	Cocoa butter, coconut oil, lard, bees wax, carnauba wax, spermaceti
4.	Volatile oil	Eucalyptus oil, clove oil, peppermint oil, lavender oil
5.	Enzymes	Pancreatin, pepsin, papain
6.	Tannins	Myrobalan, amla, bahera
7.	Protein	Gelatin, casein

Excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. Depending on the route of administration, and form of medication, different excipients may be used.

NATURAL COLORANTS

Colorants are characterized by their ability to absorb visible part of the electromagnetic spectrum (380–780 nm). For good coloring property, it has to have high enough absorption coefficient (10,000 to 40,000 $l.mol^{-1}.cm^{-1}$). Colorants could be divided by their color, chemical composition or structure, biological function in plant/organism, physical properties (solubility), etc.

CLASSIFICATION OF NATURAL COLORANTS

(Figs 2.6 and 2.7)

1. **Polyene colorants:** Polyenes are hydrocarbons with more conjugated double bonds in the chain mostly in "trans" configuration.

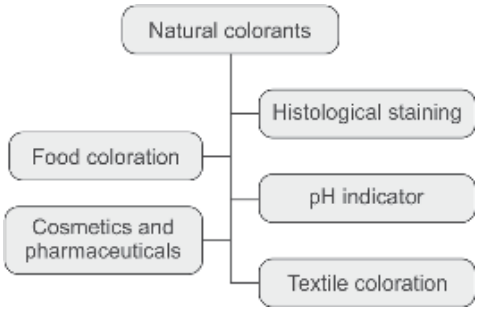


Fig. 2.6: Natural colorants and its types

Example: Crocin extract is the trade term for the yellow, water-soluble food colorant obtained from cape jasmine (*Gardenia jasminoides* L.) and from red stigmas of saffron (*Crocus sativus* L.). Curcumin is the principal color present in the rhizome of the turmeric plant (*Curcuma longa*).

2. **Chalcone colorants:** Safflower (*Carthamus tinctorius* L.) Formerly as a red dyestuff for textiles; and currently as a minor colorant by the food industry.

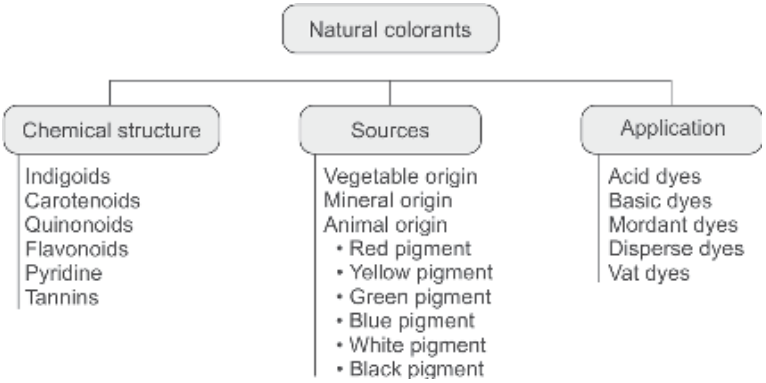


Fig. 2.7: Classification of natural colorants

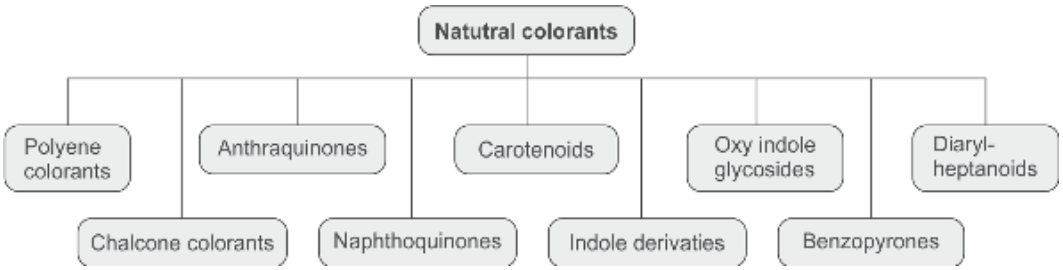


Fig. 2.8: Chemical classification of natural colorants

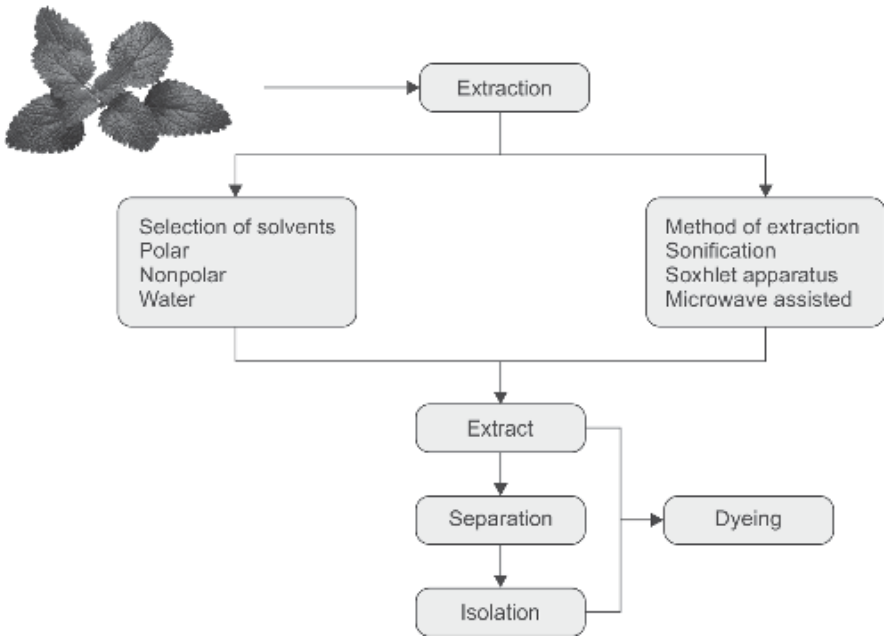


Fig. 2.9: Extraction and isolation of natural colorants

3. **Anthraquinones:** Lac obtained from *Coccus laccae* as a red dyestuff due to laccaic acid.
4. **Naphthoquinones:** Henna obtained from *Lawsonia alba* as orange dyestuff due to presence of lawsone. Walnut obtained from *Juglans nigra* as brown dyestuff due to presence of Juglone.
5. **Cartenoids:** Capsicum obtained from *Capsicum annum* have Capsanthin which have orange-red color shade. Saffron from *Crocus sativus* contain crocin which is yellow-orange dye.
6. **Indole derivatives:** Indigo (indigo tinctorial) contain blue colour dye due to compound indigotin.
7. **Oxy indole glycosides:** Beet root from *Beta vulgaris* contains betanin which is red color dye.
8. **Diarylheptanoids:** Turmeric obtained from *Curcuma longa* contains curcumin which is yellow color dye.
9. **Benzopyrones:** Logwood contains haematin is black color dye.

EXAMPLES OF NATURAL COLORANTS

Henna

Lawsonia inermis Linn, commonly known as Henna, is a shrub belonging to the Lythraceae family. It is seen as a perennial shrub in sub-tropical and tropical areas of Middle East,

Africa, Southern Asia, Northern Australia, and other semi-arid areas. It is widely used to augment beauty and as a commercial crop.

Chemical constituents: The staining property of henna is mainly attributed to a naphthoquinone compound named lawsone found in the dried leaves. The compounds in these dried leaves impart a brown color as they have chemical properties that are analogous to tannic acid and thus its name hennotannic acid. It also contains phenolic glycosides, coumarins, xanthene, flavonoids, fat and resin (Fig. 2.10).

Application: Used for cosmetic purposes as pigments to color hair and nails imparting a reddish yellow tint. Other uses are namely, in textile industries for dyeing wool and nylon, traditionally practiced medicinal plant for the treatment of various ailments.

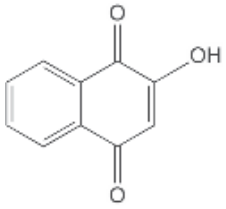


Fig. 2.10: Lawsone

Turmeric

Curcuma longa rhizome, an important tropical spice, which is a member of the ginger family Zingiberaceae. Turmeric has also attracted considerable attention over the years due to its use in the food industry as a coloring agent.

Chemical constituents: Curcumin, the major coloring principal presents in turmeric, can be extracted and used as a natural food color. Turmeric owes its characteristic yellow color to three major pigments; curcumin (50–60%), demethoxy curcumin (20–30%) and bis demethoxy curcumin (7–20%) (Fig. 2.11).

Uses: Turmeric (*Curcuma longa*) is a spice commonly used to impart yellow color at household level, mostly for spicy preparation, however, its direct use for sweet products is mostly limited due to its typical flavor and

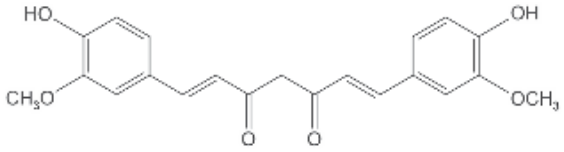


Fig. 2.11: Curcumin

taste. Turmeric and its extract have various beneficial effects on human health. All these curcuminoids are known to have antioxidant activities. Some pigments can act as both a colorant and a preservative for food. Amongst these, curcumin is an important natural colorant used in food, which has a wide range of pharmacological activities. It has antimicrobial effects against many microorganisms, especially against bacillus subtilis, *Escherichia coli* and *Staphylococcus aureus*.

NATURAL SWEETENERS (Fig. 2.12)

Natural sweetening agents are preferred over synthetic sweetening agents since they do not have any adverse impact on health. Non-saccharide natural sweetening agents are low calorific, nontoxic and super sweet (100 to 10,000 times sweeter than sugar) in nature and can overcome the problems of sucrose and synthetic sweeteners. Natural sweeteners are useful sugar substitutes for diabetic patients. The active sweet principles stored in plants can be grouped under: Terpenoids, steroidal saponins, dihydroisocoumarins, dihydrochalcones, proteins, polyols, volatile oils, etc. in nature.

Ideal properties of sweetening agents

Sweetening agents should have the following ideal properties

1. They are required to be effective when used in small concentration.
2. They must be stable at a wide range of temperature to which the formulations are likely to be exposed.
3. Prolonged use of these agents containing preparations should not produce any carcinogenic effects
4. They should have very low or non-calorific value.

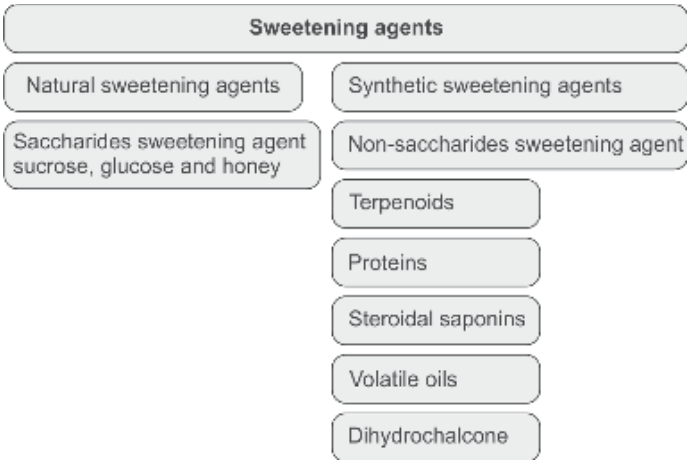


Fig. 2.12: Natural sweetners and its type

5. They should be compatible with other ingredients in formulations.
6. They should not show batch to batch variations.
7. They should be readily available and inexpensive.

SACCHARIDE SWEETENING AGENTS

Sucrose

Sucrose is a disaccharide sugar obtained mainly from the cane juice of *Saccharum officinarum* (Graminae) and from the roots of *Beta vulgaris* (Chenopodiaceae). Sucrose is most often prepared as a fine, white crystalline powder with a pleasing, sweet taste. It consists of two monosaccharides, α-glucose and fructose.

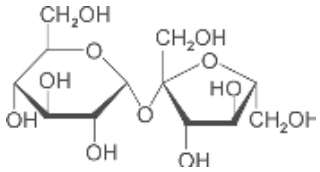


Fig. 2.13: Sucrose

Honey

Honey is a sugar secretion deposited in honeycombs by the bees *Apis indica* (Indian Bee), *Apis mellifera*, *Apis dorsata* (Rock Bee) and other species of Apis of family Apidae. The typical composition of honey is: Moisture, 17.7%; total sugars, 76.4%; ash, 0.18%; and total acid (as formic acid), 0.08%. Honey also contains tiny amounts of several compounds function as food preservative, antioxidants, including chrysin, pinobanksin, vitamin C, catalase, and pinocembrin.

Honey is essentially a solution of Leavulose (40–50%), dextrose (32–37%) and sucrose (0.2%) in water (13–20%). It is used as demulcent, sweetening agents and good nutrient to infant and patients. It is antiseptic and applied to burns and wounds.

NON-SACCHARIDE SWEETENING AGENTS

Non-saccharide sweetening agents are those, which contain substances other than saccharides as sweet principles. They contain terpenoids, proteins, dihydrochalcones, steroidal saponin, etc. as sweet principles. The non-saccharide sweeteners possess some advantages over saccharide sweeteners.

TERPENOIDS

Steviosides

Steviosides are obtained from leaves of small perennial herb *Stevia rebaudiana* Compositae. Stevioside was first isolated principle of this plant, which is 200–300 times sweeter principle than sucrose (Fig. 2.14). It also contains sweet principles such as Steviosides A and B, Steviobioside, Rebaudioside A, B, C, D, E and Dulcoside A.

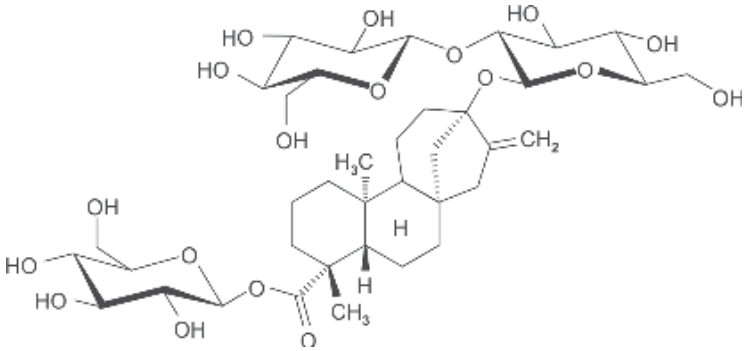


Fig. 2.14: Steviosides

DIHYDROISOCOUMARINS

Phyllodulcin

Phyllodulcin is obtained from the plant *Hydrangea macrophylla* (saxifragaceae) commonly known as amacha. This plant is indigenous to Japan, China and is found in North and South America, and temperate hills of India particularly Assam and in Himalayas.

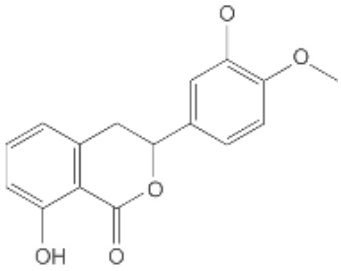


Fig. 2.15: Phyllodulcin

PROTEIN SWEETENERS

Thaumatin

The Thaumatins are a family of very sweet proteins present in the fruits *Thaumatococcus danielli* (Marantaceae). Thaumatin I and II are intensely sweet, and have 207 amino acids differ by five amino acids. Thaumatin elicits a very sweet taste that is rated to be 2000 to 10000 times sweeter than sucrose, depending on purity and concentration. Thaumatin I and II are soluble in water and dilute alcohol. Their solubility is maximal at pH 2.7–3. The sweetening power does not disappear on heating.

Miraculin

The taste-modifying protein, miraculin has the unusual property of being able to modify a sour taste into a sweet taste. *Richardella dulcifica* belonging to family Sapotaceae, a shrub native to tropical West Africa, produces red berries that have an active ingredient, glycoprotein molecule with some trailing carbohydrate chains called miraculin, a taste modifying proteins that causes citric acid, ascorbic acid, and acetic acid, which are normally sour, to perceived as sweet after the berry has been held in the mouth.

Curculin

Curculin isolated from *Curculigo latifolia*, a plant grown in Malaysia, has an intriguing property of modifying sour taste into sweet taste. In addition to this taste modifying activity, curculin itself elicits a sweet taste. It is composed of two homologous subunits designated as curculin-1, curculin-2, which share 77% identity in the amino acid sequences.

DIHYDROCHALCONES

Glycyphyllin

The sweet principle glycyphyllin is present in almost all parts of the plant smilax glycyphylla (liliaceae). Commonly, it is known as barichobchini. It is indigenous to India and found in Himalayas. It is mainly propagated through rhizomes and tuberous roots. The sweet principle is a dihydrochalcone glucoside, 100–200 times sweeter than sucrose. The

extract of shoot or almost all parts provide sweetening agent.

STEROIDAL SAPONINS

Polypodoside A

The sweet principle polypodoside A is obtained from the rhizomes of the North American plant *Polypodium glycyrrhiza* (polipodiaceae), commonly known as liquorice fern, initially, the sweet taste of the rhizomes was attributed to the presence of a sweet glycoside glycyrrhizin. This steroidal saponin glycoside on enzymatic hydrolysis with hesperindinase yields D-glucose, L-rhamnose and aglycone polypodogenin.

Osladin

European polypody fern *Polypodium vulgare* (polypodiaceae) rhizomes contain the glycoside Osladin as sweet principle. It is 300–3000 times sweeter than sucrose.

POLYOL SWEETENERS

Xylitol

Xylitol is apolyol, with a sweetening power similar to sucrose, found in fruits and vegetables. It has many advantages as a food ingredient. It does not undergo a Millard reaction, responsible for both darkening and reduction in the nutritional value of proteins. Used in combination with alcohols, sugars and amino acids, xylitol has been used as stabilizing agent for proteins during their extraction from natural membranes thus avoiding denaturation

NATURAL BINDING AGENTS

Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression as well as improving the flow qualities by the formulation of granules of derived hardness and size. The choice of a suitable binder for a tablet formulation requires extensive knowledge of the relative importance of binder properties for enhancing the strength of the tablet and also of the interactions between the various materials constituting a tablet.

Classification on the basis of their source:

1. **Natural polymer:** Starch, pregelatinized starch, gelatin, acacia, tragacanth and gums.
2. **Synthetic polymer:** PVC, HPMC, methyl cellulose, ethyl cellulose, PEG.
3. **Sugar:** Glucose, sucrose, sorbitol.

Starch

There are various types of natural polymers like starch, gums, pregelatinised starches are used as binding agent. Starches like rice starch, maize starch, potato starch, wheat starch, corn starch are well known for their binding and disintegrating properties.

Starch is also used as fillers. Starch is widely used as thickening, stabilizing, gelling and/or filling agent in many food applications and it considered as the most used excipient in pharmaceutical formulations.

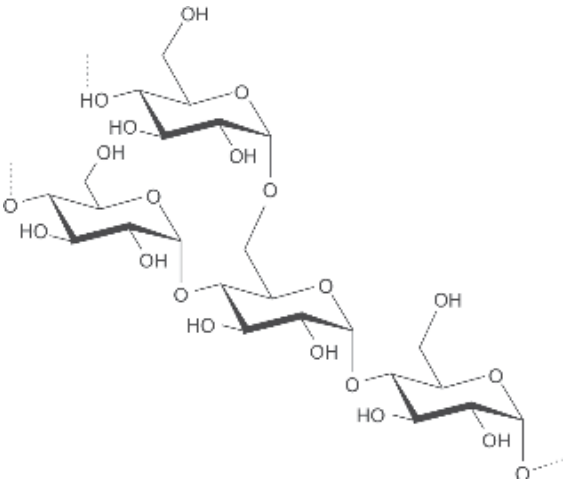


Fig. 2.16: Starch

Acacia

It is obtained from dried gummy exudation from the stems and branches of *Acacia arabica* belonging to family Leguminosae. It is white or yellowish thin flakes, odorless and bland taste. It consists of arabinose, galactose and

rhamnose. It is used as tablet binder, suspending agent, emulsifying agent, mucilage and thickener.

Natural Gums

Gums generally are polysaccharides which are polymeric in nature of natural substances obtained from woody and non-woody plant parts such as bark, seeds, sap, roots, rhizomes, fruits and leaves.

Ferula Gummosa Boiss

Ferula gummosa Boiss is one of the natural plants of Iran. The whole plant, but especially the root, contains the gum resin galbanum. The plant belonging to family Apiaceae family is growing in the north and west mountainous regions at heights 1800–3000 m above sea level. The best planting seasons are October and November. The galbanum gum has the ability to hydrate and swells in cold water.

Gum Olibanum

Gum Olibanum is the dried gummy exudation is an aromatic resin used in incense and perfumes. It is an exudate gum obtained from trees of the genus Boswellia in the family Burseraceae, particularly *Boswellia sacra*. It is also chewed like gum, but it has a stickier consistency.

NATURAL DILUENTS

Diluents are added for improving cohesion, allowing direct compression, enhance flow and adjust weight for formulation, i.e. tablets. Diluents act as fillers in pharmaceutical tablets to increase weight and improve content uniformity. Natural diluents include starches, hydrolyzed starches, and partially pregelatinized starches. Common diluents include anhydrous lactose, lactose monohydrate, and sugar alcohols such as sorbitol, xylitol and mannitol.

Lactose: It is a natural disaccharide consisting of galactose and glucose, also known as milk sugar and lactin. It is white crystalline powder, odorless and faintly sweet taste. It is freely soluble in water.

Lactose is a disaccharide derived from the condensation of galactose and glucose, which form a β-1-4 glycosidic linkage. Its systematic name is β-D-galactopyranosyl-(1→4)-D-glucose.

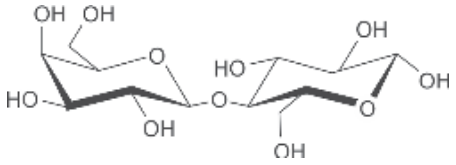


Fig. 2.17: Lactose

Mannitol

It is becoming more popular as a filler/binder in formulations because of its chemical stability, low hygroscopicity, solubility and organoleptic properties. It has favorable tableting characteristics that produce robust tablets with good disintegration. Mannitol is a versatile excipient that is ideal for the formulation development and manufacturing of a wide range of patient-friendly dosage forms.

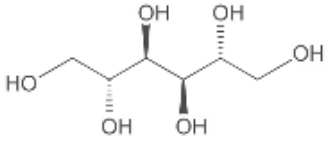


Fig. 2.18: Mannitol

VISCOSITY BUILDERS

These are substances which are added to mixture to increase the viscosity without modifying properties and stability to provide palatability and pourability. The ideal characteristics are

1. They should be non-toxic.
2. Should produce structured vehicle
3. It should have high viscosity at negligible shear during storage and low viscosity at high shearing rate during pouring.
4. It should exhibit yield stress.
5. It should be compatible with other excipients.

Carrageenan

Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides, which are obtained by extraction from certain species of red seaweeds. Carrageenan has no nutritional value and is used in food preparation for its gelling, thickening, and emulsifying properties and in pharmaceutical applications. The chemical reactivity of carrageenan is primarily due to their half-ester sulfate groups which are strongly anionic, being comparable to inorganic sulfate.

Xanthan Gum

Xanthan gum is a polysaccharide with many industrial uses, including as a common food additive. It is an effective thickening agent and stabilizer to prevent ingredients from separating. It can be produced from simple sugars using a fermentation process, and derives its name from the species of bacteria *Xanthomonas campestris*. Xanthan gum is a food thickener made from bacteria that infect numerous plants. It is an ingredient in a wide variety of foods, as well as products such as toothpaste. Though it may offer some health benefits, it is used primarily to change the texture of food, not for any specific health need.

NATURAL DISINTEGRANTS

Disintegrants are substances added to the drug formulation that increase the breakup of the tablet or capsule into smaller particles in aqueous environment that dissolve more rapidly than in the absence of disintegrates. Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets and contents of capsules into smaller fragments for quick dissolution.

Ispaghula Husk Mucilage

Ispaghula husk consists of dried seeds of the plant known as *Plantago ovata*. Mucilage of *Plantago ovata* has different characteristics like binding, disintegrating and sustaining properties. Mucilage can be used as superdisintegrant to formulate fast dissolving tablets because it has very high percentage of swelling index as compared to the other super disintegrating agents. The rate at which swelling develops and significant force of swelling also determine its disintegrating efficiency.

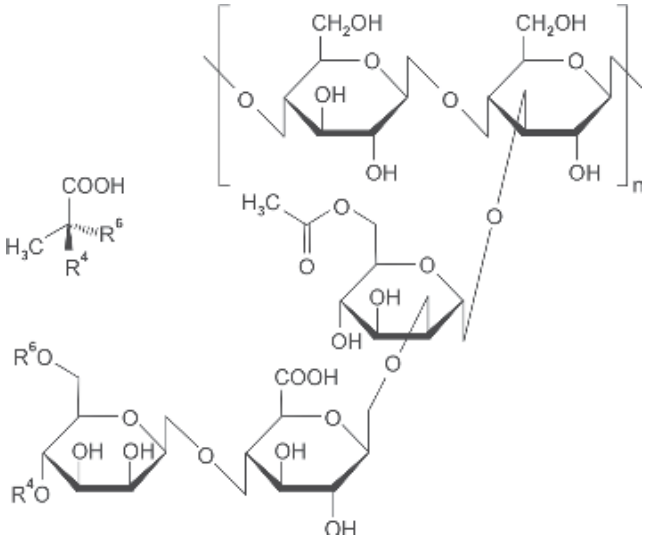


Fig. 2.19: Xanthan gum

Fenugreek Seed Mucilage

Trigonella foenum-graecum (leguminous family) is an herbaceous plant. It has found wide applications as a food, a food additive, and as a traditional medicine. The leaves and both the ripe and unripe seeds of *Trigonella foenum-graecum* are used as vegetables. Fenugreek has been used in treating dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, colic flatulence, dysentery, diarrhoea, gout, and diabetes. It is also used as gastro protective, antiurolithiatic, diuretic, antidandruff agent, anti-inflammatory agent and as antioxidant. The seed is stated to be a tonic.

FLAVORING AGENTS

Flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which involve a combination of physiochemical and physiological actions that influence the perception of substances.

FORMULATION DEVELOPMENT OF HERBAL MEDICINAL PRODUCTS

Dosage forms are the means by which drug molecules or plant parts are delivered to sites of action within the body. There are various routes of administration of dosage forms which include oral, rectal, topical, parenteral, respiratory, nasal and ophthalmic. The quality control and stability testing are the specific protocols for finished dosage forms. Herbal medical products are finished and labelled products mainly contains active ingrediants/ phytoconstituents which is obtained from aerial or underground parts of plants. Herbal drug preparations can be obtained by extraction, distillation, expression, fractionation, purification, concentration or fermentation. These comprise comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates.

The herbal medicines and preparations are extracted to obtain extractive isolates which are extremely complex multicomponent mixtures, as opposite to synthetic drugs that are most commonly a single pure compound. For production of herbal remedies following steps to be undertaken collecting of medicinal plants from spontaneous flora and plantation cultivation, obtaining extractive isolates, and their characterization. Opportunely, the production of herbal medicines is largely modernized and well-defined in all sections.

There are a number of guidelines that recommend standards in all phases of making herbal medicines such as

1. The European Medicines Agency guidelines for the quality of herbal medicines.
2. The WHO guidelines provide standards and guidelines for good agricultural practices, good laboratory practices, and so on.

The development of new, sophisticated analytical, and technological methods and procedures within the development and characterization of extractive isolate has significantly enhanced the quality of the final plant products.

STABILITY STUDIES OF FINISHED HERBAL PRODUCTS

The World Health Organization (WHO) recommends that stability data be provided to support the shelf-life proposed for finished herbal products under the specified conditions of storage. The shelf-life of a product is the period during which it remains within acceptable chemical, physical and microbiological stability if stored correctly. The expiry date is represented on the product to indicate the end of the shelf life. Finished herbal products are unique compared to synthetic products due to the varied nature of constituents that may be present even in an herbal product with only one herbal ingredient. The herbal material, in its entirety, is normally regarded as the active ingredient and a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Constituents (markers) for stability determina-

tion in herbal products may be categorized as chemical, analytical and active markers.

Chemical markers may be defined as chemically defined constituents or groups of constituents of an herbal medicinal product which are of interest for quality control purposes regardless of whether they possess any therapeutic activity. The quantity of a chemical marker can be an indicator of the quality of an herbal medicine. Chemical markers may be used to evaluate product quality and stability over time and determine the recommended shelf life. Analytical markers are the constituents or groups of constituents that serve solely for analytical purposes. Active markers are the constituents or groups of constituents that contribute to therapeutic activities.

STABILITY DETERMINATION OF HERBAL MEDICINAL PRODUCTS

The principle of a stability study is to provide evidence that an active substance or finished product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The importance of stability testing is to evaluate the efficacy of a drug; provide background information during the development phase of the product or drug discovery; develop suitable packaging information for quality, strength, purity and integrity of a product during its shelf-life. Mechanisms that may indicate a change in stability include loss of activity; change in concentration of active component; alteration in bioavailability of product; loss of content uniformity; loss of elegance; formation of toxic degradation products and loss of packaging integrity. It is difficult to develop analytical methods for herbal medicines due to the presence of phytochemical constituents which may be susceptible to enzymatic breakdown of these plant metabolites. Predictable chemical changes in herbal products include hydrolysis; oxidation (especially in fixed, volatile and essential oils); racemization; geometric isomerization and polymerization.

PROCESS OF DRUG DEVELOPMENT

A typical drug development process from herbal medicine broadly includes the following aspects:

1. Isolation of bioactive ingredients and synthetic modifications of it.

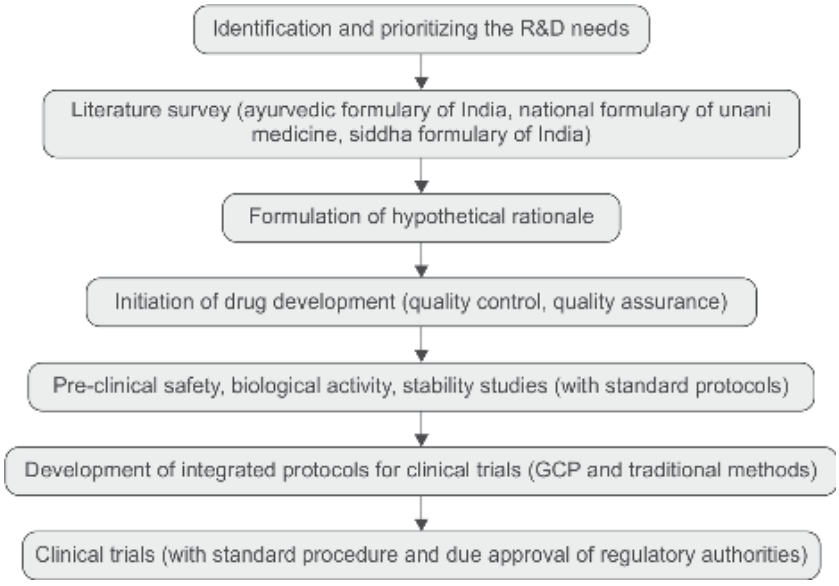

Identification and prioritizing the R&D needs
Literature survey (ayurvedic formulary of India, national formulary of unani medicine, siddha formulary of India)
Formulation of hypothetical rationale
Initiation of drug development (quality control, quality assurance)
Pre-clinical safety, biological activity, stability studies (with standard protocols)
Development of integrated protocols for clinical trials (GCP and traditional methods)
Clinical trials (with standard procedure and due approval of regulatory authorities)

Fig. 2.20: Process of ayurvedic drug development

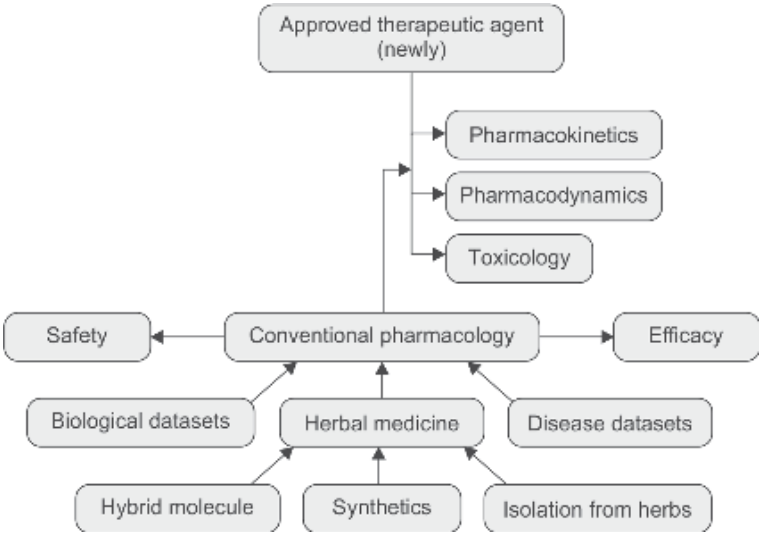


Fig. 2.21: Standard operating procedure (SOP) for drug development

2. Evaluation of safety and efficacy.
3. Regulatory approval of the therapeutic agent in case of new drug.
4. Clinical trials.

The drug should be subjected to drug standardization followed by biological activity, preclinical studies and safety studies, etc.

EVALUATION CRITERIA

PLANT EXTRACT

1. Color
2. Odor
3. Taste (if necessary)
4. Loss on drying at 105°C/moisture content
5. Total ash
6. Acid-insoluble ash
7. Water-soluble extractives
8. Alcohol-soluble extractives
9. pH
10. Bulk density
11. Tap density
12. Volatile oil content (if present)
13. Residual solvent
14. Chemical test for secondary metabolites, e.g. alkaloids, terpenoids, flavonoids, glycosides, soponins, etc.
15. TLC/HPTLC/HPLC with marker(s)
16. Test for heavy/toxic metals (lead, cadmium, mercury, arsenic) (limits as per ASU Pharmacopoeia)
17. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (Limits as per ASU pharmacopoeia)
18. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count
    (Limits as per ASU pharmacopoeia)
19. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
20. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
21. Shelf life

ARKA/DISTILLATES

1. Color
2. Odor
3. Specific gravity at 25°C
4. Boiling point
5. Assay for essential oil (percentage of essential oil)

6. Refractive index
7. Optical rotation
8. Viscosity
9. TLC/HPTLC/GLC/GC-MS (any one or all)
10. Total acidity
11. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
12. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (Limits as per ASU pharmacopoeia)
13. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count
    (Limits as per ASU pharmacopoeia)
14. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (Limits as per ASU pharmacopoeia)
15. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
16. Shelf life

AYURVEDIC FORMULATIONS

Asava and Arishta (Fermented Liquids)

1. Color
2. Odor
3. pH
4. Specific gravity at 25°C
5. Boiling point
6. Refractive index
7. Optical rotation
8. Viscosity
9. Total solids
10. Alcohol content
11. Reducing sugar
12. Non-reducing sugar
13. TLC/HPTLC/ GC-MS (any one or all)
14. Test for methanol
15. Total acidity
16. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
17. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
18. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count
    (limits as per ASU pharmacopoeia)
19. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
20. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
21. Shelf life

Avaleha/Leham/(Confectionary/Semi-Solid)

1. Color
2. Odor
3. Taste
4. Consistency
5. Loss on drying at 105°C/moisture content
6. Total ash
7. Acid-insoluble ash
8. Alcohol-soluble extractive
9. Water-soluble extractive
10. pH (10% aqueous extract)
11. Total acidity
12. Specific gravity at 25°C
13. Total solid content
14. Fat content
15. Reducing sugar/non-reducing sugar
16. Total sugars
17. Assay for major ingredients/major constituents of main ingredients
18. TLC/HPTLC/HPLC/LC-MS (any one or all)
19. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)

20. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
21. Microbial contamination
    Total viable aerobic count, *enterobacteriaceae,*
    Total fungal count
    (limits as per ASU pharmacopoeia)
22. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
23. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
24. Shelf life

Churna (Fine Powder)

1. Color
2. Odor
3. Foreign matters
4. Powder microscopy
5. Particle size (80–100 mesh for cuma; 40–60 mesh for kvatha cuma)
6. Loss on drying at 105°C/moisture content
7. Total ash
8. Acid-insoluble ash
9. pH (5% aqueous extract)
10. Water-soluble extractive
11. Alcohol-soluble extractive
12. Bulk density and tap density
13. Assay for specific ingredients/constituents group of compounds (if possible)
14. TLC/HPTLC/HPLC with markers (any one or all)
15. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
16. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
17. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count
    (limits as per ASU pharmacopoeia)
18. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
19. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
20. Shelf life

Lepa/Malhara/Medicated Wax/Cream/Poultice

1. Color
2. Odor
3. Viscosity (if in the form of flowing material)
4. Rancidity test
5. Microscopy (if powdered drugs incorporated)
6. Particle size (if powdered drugs incorporated) of the ingredients
7. Total acidity
8. TLC/HPTLC/GC/GC-M S/HPLC (any one or all)
9. Assay (wherever possible)
10. Uniformity of content
11. pH
12. Thermal stability
13. Total fat content
14. Loss on drying at 105°C/moisture content
15. Spreadibility
16. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
17. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
18. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count (limits as per ASU pharmacopoeia)
19. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
20. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
21. Shelf life

Tailas/ Ghritas/Thylam/Nei (Medicated Oils and Ghee)

1. Color
2. Odor
3. Rancidity
4. Specific gravity/weight/ml
5. pH value
6. Loss on drying at 105°C/moisture content
7. Congealing point
8. Refractive index
9. Viscosity
10. Iodine value
11. Saponification value
12. Unsaponifiable matter (percentage of)
13. Acid value
14. Peroxide value
15. Free fatty acids (percentage of)
16. Total fatty matter (percentage of)
17. Mineral oil test (it should be negative)
18. GLC/TLC/HPTLC/HPLC/GC-MS (any one of all)
19. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
20. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
21. Microbial contamination
    Total viable aerobic count, *enterobacteriaceae*
    Total fungal count (limits as per ASU pharmacopoeia)
22. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
23. Aflatoxins, (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
24. Shelf life

SOLID DOSAGE FORMS

Vati/Gutika/Vadagam (Tablet/Pills)

1. Color
2. Taste
3. Odor
4. Microscopic characters (if vegetable parts are used as ingredients)
5. pH (5% aqueous extract)
6. TLC/HPTLC/HPLC/LC-MS (any one of all)
7. Loss on drying at 105°C/moisture content
8. Friability
9. Hardness
10. Uniformity of weight
11. Disintegration time (not more than 35 minutes except guggulu)
12. Total ash
13. Acid-insoluble ash
14. Alcohol-soluble extractive
15. Water-soluble extractive
16. Total sugar (if added)
17. Reducing sugar/non-reducing sugar (if added)
18. Assay (active constituents of major ingredients) (if available)
19. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
20. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
21. Microbial contamination
    Total viable aerobic count, *enterobacteriaceae*
    Total fungal count (limits as per ASU pharmacopoeia)
22. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa*
    (limits as per ASU pharmacopoeia)
23. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)

CAPSULES

- Weight variation
- Content uniformity
- Disintegration test
- Moisture permeation test
- Stablility tests, determination of shelf life

GRANULES

- Flow properties

POWDERS

- Particle size analysis
- Angle of repose
- Bulk density
- Tapped density
- Hausner's ratio
- Flowability

SEMISOLID DOSAGE FORMS

Ointments

- Test of rate of absorption
- Test of rate of penetration
- Test of rate of drug release
- Test of rheological properties
- Test of content uniformity
- Test of preservative efficacy

Creams

- Rheology
- Sensitivity
- Suppositories
- Appearance
- Physical strength
- Melting range
- Uniformity of drug content
- Softening time

LIQUID DOSAGE FORMS

Non-sterile Liquid Dosage Forms

Syrups

1. Color
2. Odor
3. Taste
4. Viscosity
5. pH
6. Total solids
7. Reducing sugars/non-reducing sugars
8. Total sugars
9. Specific gravity at 25°C
10. TLC/HPTLC/HPLC/LC-MS (any one or all)
11. Test for heavy/toxic metals
    Lead, cadmium, mercury, arsenic (limits as per ASU pharmacopoeia)
12. Pesticide residue
    Organochlorine pesticides, organophosphorus pesticides, pyrethroids
    (limits as per ASU pharmacopoeia)
13. Microbial contamination
    Total viable aerobic count
    Enterobacteriaceae
    Total fungal count (limits as per ASU pharmacopoeia)
14. Test for specific pathogen
    Escherichia coli, salmonella spp., *Staphylococcus aureus, Pseudomonas aeruginosa* (limits as per ASU pharmacopoeia)
15. Aflatoxins (B_1 B_2 G_1 G_2) (limits as per ASU pharmacopoeia)
16. Shelf life

STERILE LIQUID DOSAGE FORMS

Parenterals

- Leaker test
- Pyrogen test
- Sterility test
- Particulate evaluation
- Weight variation or uniformity of content

Eye Drops

- Test for sterility
- Test for ocular toxicity and irritation
- Clarity
- pH
- *In vitro* diffusion studies
- Determination of viscosity

Nasal Spray

- Appearance, color and clarity
- Drug content
- Droplet size distribution
- Foreign particulates

- Microbial limits
- Net content and weight loss (stability)
- Leakage testing
- pH

COSMETICS

- Lipsticks
- Thixotropic characters
- Breaking point
- Melting point

NOVEL DRUG DELIVERY SYSTEMS

Transdermal Patches

- Thickness
- Uniformity of weight
- Drug content determination
- Content uniformity test
- Moisture content
- Moisture uptake
- Flatness
- Tensile strength
- Shear strength properties

CONCLUSION

Herbal products have gained wide acceptance in both developing and advanced countries and are being produced in commercial quantities. The stability of these herbal products is of paramount importance to assure product quality, safety and efficacy. It is expected that herbal product manufacturers will apply the necessary protocols and techniques to achieve and maintain the stability of their products during manufacture, storage, transportation and usage.

CHAPTER 3

Herbal Formulation Based Novel Drug Delivery System

HERBAL CONVENTIONAL FORMULATIONS

Recently reports of trade and commerce suggest that herbs and its products are presently used for variety of purposes. In recent years, the increasing demand for herbal medicines is being fueled by a growing consumer interest in natural products. The herbs treated by various methods squeezing, steaming, roasting, decocting or infusing in water, extracting with alcohol, or sweetening and baking with honey result as herbal products.

Examples: Juices, tinctures, decoctions, infusions, fums, fixed oils, essential oils, and resins. The herbal preparations may be subjected to number of physical, chemical, or biological processes, including pulverization, extraction, distillation, expression, fractionation, purification, concentration, or fermentation, the phytotherapeutic formulations may also be referred to as drugs or botanicals, or when taken orally to provide health benefits, they may be called dietary supplements.

Herbal medicines: Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. Herbal medicines are plant derived materials and preparations with therapeutic or other human health benefits, which contain either raw or processed ingredients from one or more plants, inorganic materials or animal origin. In 1966, WHO has issued guidelines for the assessment of herbal medicines, it includes basic criteria for the evaluation of quality, safety and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations and manufacturers in assessing documentation, submissions and dossiers in respect of products.

The conventional dosage forms, including prolonged-release dosage forms, are unable to satisfy for both holding the drug component at a distinct rate as per directed by the requirements of the body, all through the period of treatment, as well as directing the phytoconstituents to their desired target site to obtain an utmost therapeutic response.

Categorization of Herbal Medicines

Traditional herbal medicines are defined as herbal medicines (single or mixture of herbs) that have been widely used, supported by well-established safety and efficacy data, or have been used within the local community for a minimum period of 15 years. This category would also include traditional medicine formulations to which minor changes have been made. Herbal medicines that are not indigenous to the Eastern Mediterranean Region, e.g. ginseng, could also be included.

Phytotherapeutic agents or phytomedicines are standardized herbal preparations consisting of complex mixtures of one or more plants, which are used in most countries for management of various diseases. According to the WHO definition, herbal drugs contain as active ingredients plant part or plant materials in the crude or processed state plus certain excipients, i.e. solvents, diluents or preservatives. The active principles responsible for their pharmacological actions are not usually known.

Comparison of Conventional Dosage Form and Novel Drug Delivery

Conventional dosage forms, including prolonged-release dosage forms, are unable to fulfil the ideal requirements of novel carriers such as ability to deliver the drug at a rate directed by the penury of the body and to transmit the active entity of herbal drug to the site of activity. For good bioavailability, natural products must have a sound balance between hydrophilicity (for dissolving into the gastrointestinal fluids) and lipophilicity (to cross lipidic biomembranes). Many phyto-constituents such as polyphenolics have good water solubility, but are poorly absorbed either due to their multiple-ring large-sized particles which cannot be soaked up by simple diffusion or referable to their poor miscibility with oil and other lipids, severely restricting their power to reach across the lipid-rich outer membranes of the enterocytes of the little bowel. Thus, the nano-sized NDDSs of herbal drugs have a potential future for enhancing the natural process and overwhelming problems related with plant medicines. Novel herbal drug carriers cure particular disease by targeting just the affected zone inside a patient's body and transporting the drug to that region. NDDS is advantageous in giving up the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with an increase in bioavailability of drugs. In novel drug delivery technology, control of the dispersion of the drug is achieved by incorporating the drug in carrier system or in modifying the social organization of the drug at the molecular level. Incorporation of herbal drugs in the delivery system also aids to increase in solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to take anticancer agents by increasing amount of drug in tumor area and decrease the exposure or accumulation of drug in normal cells/tissues, thereby preventing tissue toxicity effects. The phytosomal carriers have been considered for effective delivery of herbal extracts of ginseng (*Ginkgo biloba*), etc. Direct binding of phosphatidylcholine to herbal extract components led to better absorption characteristics as compared to conventional delivery of herbal infusions. Other vesicular assemblies such as microspheres, animations, and polymeric nanoparticles have been shown beneficial to carry herbal components.

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. For a long time, herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex poly herbal systems such as nanoparticles, micro emulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on. Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone.

In phytoformulation research, developing nano-sized dosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes, and nano-

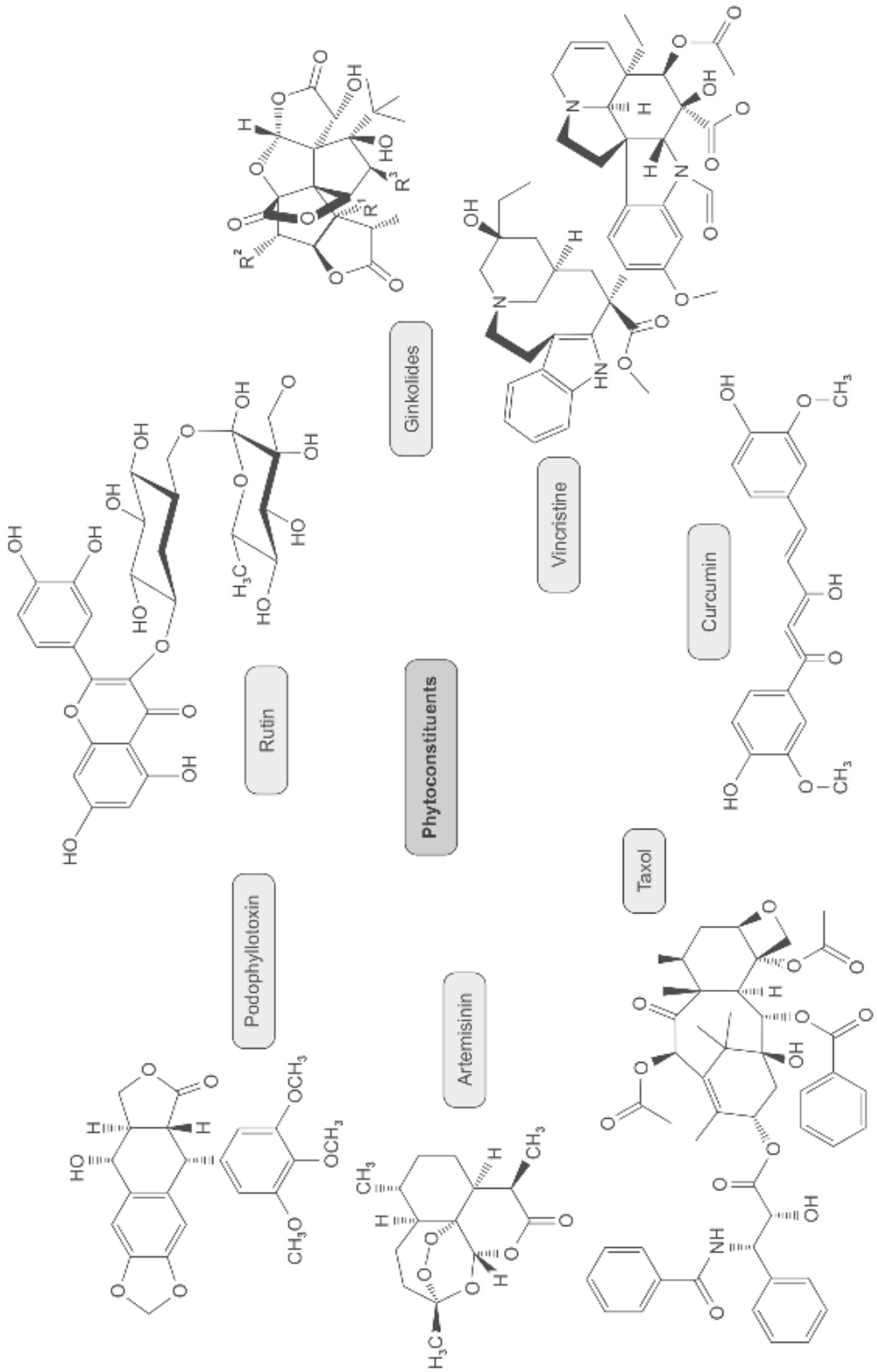


Fig. 3.1: Phytoconstituents delivered through NDDS

emulsion) has a number of advantages for herbal drugs, including:

1. Enhancement of solubility
2. Increased bioavailability
3. Protection from toxicity
4. Enhancement of pharmacological activity
5. Enhancement of stability
6. Improving tissue macrophage distribution
7. Sustained delivery
8. Protection from physical and chemical degradation.

Thus, the nano-sized NDDSs of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with the plant medicines.

Incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation or presystemic metabolism and serious side effects by accumulation of drugs to the nontargeted areas and improves the ease of administration in the pediatric and geriatric patients.

Phytochemical Bioavailability and Efficacy in Preventing Chronic Diseases

Since ancient times, plant-derived compounds have been a great source of materials used in beneficial medical treatments. The several other factors could also play a role in limiting bioavailability, such as solubility of the compound, stability due to gastric and colonic pH, metabolism by gut microflora, absorption across the intestinal wall, active efflux mechanism and first-pass metabolic effects. Examples of compounds that are only sparingly water-soluble include ellagic acid, curcumin and resveratrol. A promising approach to overcome low bioavailability and systemic toxicity is the application of drug-loaded nanosized drug carriers, such as polymeric nanoparticles (NPs), liposomes, dendrimers and micelles. NPs may enhance the oral bioavailability of poorly soluble drugs and the tissue uptake after parenteral administration, through adherence to the capillary wall. They also enhance the delivery of certain drugs across membranes. Being small in size, NPs have the potential to leave the vascular system and enter sites of inflammation. The NP size limitation for crossing different biological barriers is dependent on the tissue, target site and circulation. The distinct advantages of liposomes are their ability to encapsulate various materials and their structural versatility. Liposomes can encapsulate drugs with widely varying solubility or lipophilicity, either entrapped in the aqueous core of the phospholipid bilayer or at the bilayer interface. Liposomes are able to deliver drugs into cells by fusion or endocytosis, and practically any drug, irrespective of its solubility, can be entrapped into liposomes. Despite the many advantages of liposomes, including safety and biocompatibility, their main drawback as nanocarriers is their instability in plasma. The polymeric micelle system, owing to its solubilization, selective targeting, P-glycoprotein inhibition and subcellular localization properties, has received growing scientific attention as an effective drug carrier. Niosomes are a promising vehicle for drug delivery, and since they are non-ionic, they are less toxic and improve the therapeutic index of drugs by restricting their action to target cells. The characteristics of the vesicle formulation are variable and controllable. Niosomes are osmotically active, stable and increase the stability of the entrapped drug. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in an external non-aqueous phase.

Cyclodextrins (CDs) enhance bioavailability of insoluble drugs by increasing drug solubility and dissolution. They also increase the permeability of insoluble, hydrophobic drugs by making the drug available at the surface of the biological barrier (e.g. skin and mucosa) from whence it partitions into the membrane without disrupting the lipid layers

of the barrier. CDs enhance the bioavailability of insoluble drugs by molecular dispersion, protection from degradation, and delivery to the surface of the intestinal wall.

Implants of drug-loaded polymers, either as millirods, pellets or microspheres, are able to deliver drugs for prolonged periods. The benefits of this subcutaneous implantation include greater assurance of patient compliance, which then leads to better therapeutic outcome, particularly for chronic medication (Fig. 3.2.)

Phytochemicals with Low Bioavailability

Most of the **biologically active polyphenolic phytoconstituents** are associated with the problem of either:

- Poor absorption
- Poor permeation
- Poor availability

Flavonoids

Problem: Good water solubility, but they are poorly absorbed.

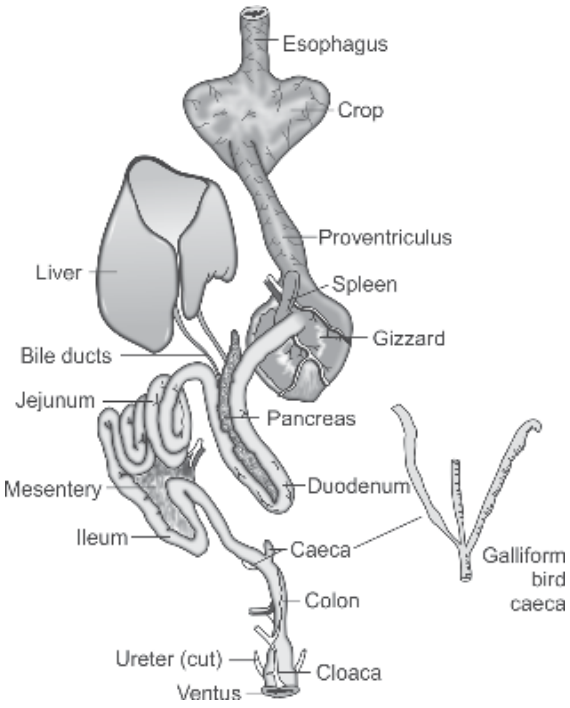


Fig. 3.2: Site of bioavailability of herbal drugs

Curcumin

Problem: Insoluble in water, highly unstable undergoing rapid hydrolytic degradation.

Andrographolides

Problem: High lipophilicity and low aqueous solubility and poor bioavailability.

Rutin

Problem: Poor bioavailability and is not significantly absorbed before 2 hours, peak plasma concentrations—6 hours.

Paclitaxel (for malignancies)

***Problem*:** Limited aqueous solubility

Formulated with mixture of cremophor EL (formulation vehicle used for poorly water soluable drugs) and ethanol.

Thus, patients receive cremophor EL, resulting in plasma levels of cremophor EL. cremophor EL causes (severe) hypersensitivity.

Artemisinin

Problem: Low bioavailability after oral administration probably due to incomplete absorption, T_{max}—2 to 3 hours post dose; elimination is rapid.

Ginsenoside

Problem: Pre-systemic elimination (degradation in acidic condition), low solubility and low bioavailability.

Etoposide (anticancers).

Problem: Bioavailability limitation, because of poor water solubility.

TYPES OF NOVEL DRUG DELIVERY

New herbal drug delivery system includes different types of expressions such as mouth-dissolving tablets, liposomes, phytosomes, pharmacosomes, museums, nanoparticles, microspheres, transfersomes, ethosomes, transdermal drug delivery system (TDDS), and proniosomes (Figs 3.3 and 3.4).

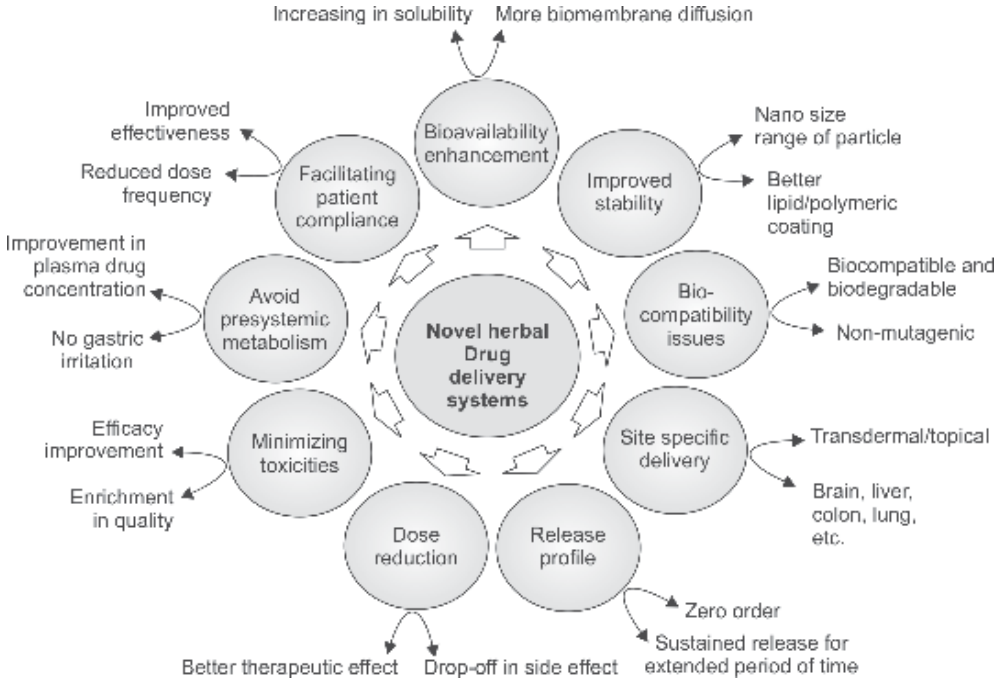


Fig. 3.3: Salient features of novel drug delivery system

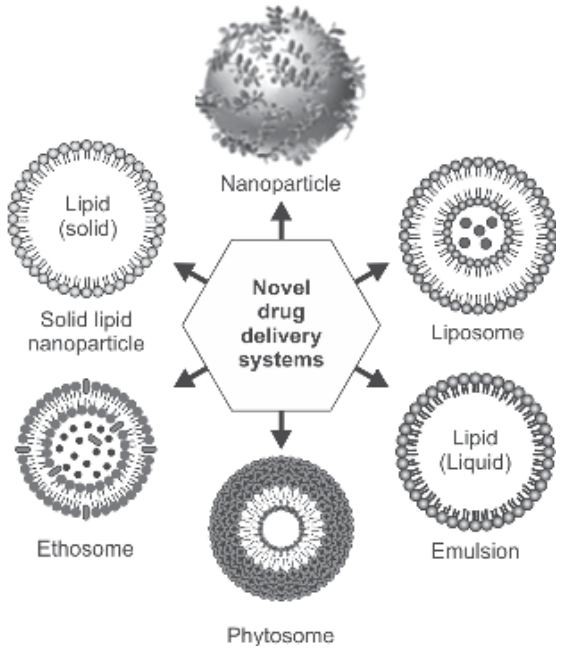


Fig. 3.4: Types of novel drug delivery systems

PHYTOSOMES

The term *phyto* means plant while *some* means cell-like. Phytosome is vesicular drug delivery system in which phyto constituents of herb extract surround and bound by lipid (one phyto-constituent molecule linked with at least one phospholipid molecule).

Most of the bioactive constituents of phytomedicines are flavonoids, which are poorly bioavailable when taken orally. Water-soluble phytoconstituent molecules (mainly polyphenols) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Phytosomes are more bioavailable as compared to simple herbal extracts owing to their enhanced mental ability to skip through the lipid-rich biomembranes and finally arriving to the origin. The lipid-phase substances employed to make phytoconstituents lipid compatible are phospholipids from soy, mainly phosphatidylcholine. Phytosomes protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria and because of which they show better absorption which produces better bioavailability and improved pharmacological and pharmacokinetic parameters than conventional herbal extract.

Advantages of Phytosomes

1. Increased bioavailability due to phospholipid complex.
2. Improved absorption in GIT.
3. Increased bioavailability causes improved therapeutic effect.
4. Less dose requirement due to high bioavailability.
5. Higher stability.
6. High lipophilicity causes high penetrability, henceforth used in cosmetics over liposomes.
7. Greater clinical benefits.
8. Phosphatidylcholine acts as liver protective other than a carrier.

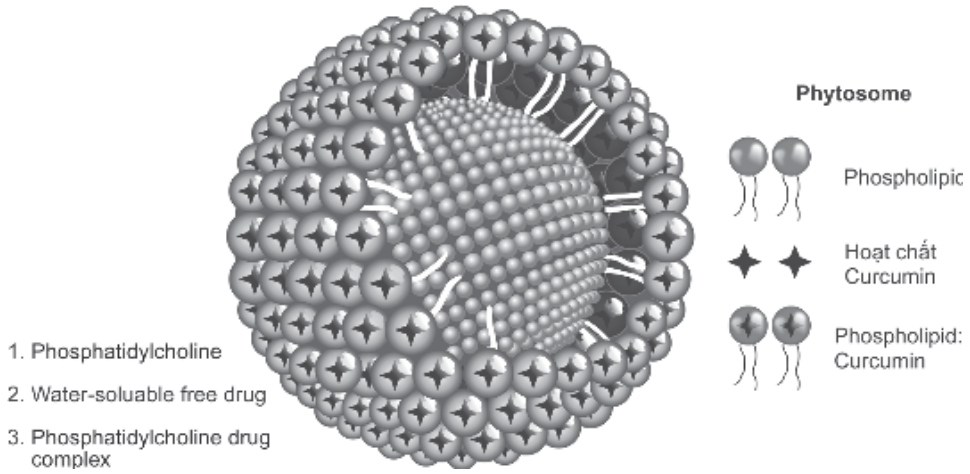


Fig. 3.5: Phytosomes

Table 3.1: Herbal formulations in phytosomal drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Crataegus sp	Nutraceutical	Used for heart disease or high blood pressure
Ginkgo biloba	Cardioprotective	Antioxidant
Thea sinensis	Nutraceutical systemic antioxidant	For protection against cancer and damage to cholesterol
Curcuma species	Anticancer antioxidant	Increase bioavailability and antioxidant activity
Ginkgo biloba	Anti-skin ageing agent	Protects brain and vascular lining
Silybin	Hepatoprotective	Antioxidant for liver and skin
Quercetin	Antioxidant anticancer	Treatment of cancer
Vitis vinifera	Nutraceutical, systemic antioxidant	In treatment of diabetes, and protects against heart disease
Olea europaea	Anti-inflammatory activity	Inhibit oxidation of LDL cholesterol
Epigallocatechin	Nutraceutical, systemic antioxidant, anticancer	Increase absorption

LIPOSOMES

Liposomes are concentric bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. The name liposome is derived from two Greek words: '*Lipos*' meaning fat and '*Soma*' meaning body. These are microparticulate or colloidal carriers, usually 0.05–5.0 μm in diameter which forms spontaneously when certain lipids are hydrated in aqueous media.

The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely pass around or float into their interior. They can carry one, several, or multiple concentric membranes. Liposomes are constructed of polar lipids, which are characterized by having a lipophilic and hydrophilic group of the same molecules. On interaction with water, polar lipids self-layup and form self-organized colloidal particles. Liposome-based drug delivery systems offer the potential to raise the therapeutic index of anticancer agents, by increasing the drug concentration in tumor cells or by lessening the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon or by utilizing targeting strategies.

The primary advantages of using liposomes include:

1. High biocompatibility.
2. The easiness of preparation.
3. The chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds.
4. The simple modulation of their pharmacokinetic properties by varying the chemical composition of the player components.
5. Provides selective passive targeting to tumor tissues (liposomal doxorubicin).
6. Increased efficacy and therapeutic index.
7. Increased stability via encapsulation.
8. Reduction in toxicity of the encapsulated agents.
9. Site avoidance effect.
10. Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
11. Flexibility to couple with site specific ligands to achieve active targeting.
12. Biodegradable and flexible.
13. Can incorporate micro and macro molecules.
14. Can carry both water and lipid soluble drugs.

A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. A liposome does not necessarily have lipophobic contents, such as water, although it usually does. Liposomes are artificially prepared vesicles made of lipid bilayer.

Table 3.2: Herbal formulations in liposomal drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Curcuma longa	Antitumor, antioxidant, antiplatelet aggregation and anti-inflammatory	Improved intravenous delivery of curcumin to tissue macrophages
Camellia sinensis	Chemopreventive, anticarcinogenic, antiviral, antioxidative, antiobesity, anti-inflammatory, antidiabetic, antimutagenic, activities	Improved loading and *in vivo* deposition of catechins
Quercetin and rutin	Hemoglobin	Hemoglobin binding
Silybus marianum	Hepatoprotective agent	Improved permeation and stability of silymarin
Catechins	Antioxidant and chemoprotective	Increase permeation through skin
Paclitaxel	Anticancer agent	Improves entrapment efficiency

Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membranes, for example, by sonication.

Nanoparticles

Nanoparticles are efficient delivery systems for the delivery of both hydrophilic and hydrophobic drugs. Nanoparticles are the submicron-sized particles, ranging 10–1000 mm. The major goal behind designing nanoparticle as a delivery arrangement is to control particle size, surface properties, and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices. The nanospheres have a matrix type structure in which the active ingredient is dispersed throughout (the molecules), whereas the nanocapsules have a polymeric membrane and an active ingredient core. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines compared with the respective crude drugs preparations.

NIOSOMES

Niosomes are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. Niosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility. In such therapeutic applications, important advantages of using niosomes are as follows.

Advantages of Niosome

1. Niosomes are biodegradable, biocompatible, non-toxic and non-immunogenic.
2. Niosomes are able to encapsulate large amount of materials in a small volume of vesicles.
3. Niosomes have better patient adherence and satisfaction and also better effectiveness than conventional oily formulations.
4. Niosomes can entrap wide range of chemicals (hydrophilic, lipophilic and amphiphilic drugs) due to its unique structure.
5. The characteristics of niosome such as shape, fluidity and size can be easily controlled by changing in structural composition and method of production.
6. Niosomes can be prescribed via different administration routes such as oral, parenteral and topical, etc. with different dosage forms such as semisolids, powders, suspensions.

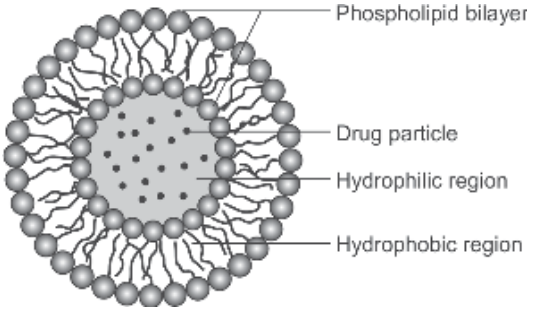


Fig. 3.6: Structure of niosomes

Table 3.3: Herbal nanoparticulate drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Berberine	Antitumor	Sustained release of drug
Artemisinin	Anticancer	Sustained release of drug
Taxel	Anticancer	Enhanced bioavailability and sustained release of drug
Curcuminoids	Anticancer and antioxidant	Prolonged release of curcuminoids
Narigenin	Hepatoprotective	Improves solubility

Table 3.4: Herbal formulations in niosomal drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Colchicine	Rheumatic complaints	Prolonged release profile
Silymarin	In liver and gallbladder disorder	Increase drug bioavailability

7. Due to chemical stability of structural composition, the storage of the niosome is easy.
8. It has ability to reduce systemic toxicity by encapsulation of treatment agents and minimize clearance of such agents from the body by slow drug release.

PRONIOSOMES

Proniosome gel system is step forward to niosome, which can be utilized for various applications in delivery of actives at desired site. Proniosomal gels are the formulations, which on *in situ* hydration with water from the skin are converted into niosomes. Proniosomes are water-soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media.

Transdermal Drug Delivery System

TDDS has been an increased stake in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as comfortably as for systemic delivery of drugs. However, they did not have had such expected success with other drugs. But, immense potential lies in transdermal drug as future smart drug delivery devices. Transdermal delivery system provides the advantage of controlled drug delivery, enhanced bioavailability, reduction in side effects, and easy application. Thus, this delivery system avoids the first-pass metabolism of the drug without the annoyance associated with injection; moreover, the scheme offers a prolonged drug delivery with infrequent dosing via zero-order kinetics and the therapy can be easily fired at any time.

TRANSFERSOMES

The term and concept of transfersome were introduced in 1991 by Gregor Cevc. The name means carrying body, and is derived from the Latin word 'transferre' meaning to carry across, and the Greek word soma for body. Transfersomes are specially optimized particles or vesicles that can respond to an external stress by rapid and energetically inexpensive, shape transformations. The development of novel approaches such as transfersomes have immensely contributed in overcoming problem faced by transdermal drug delivery such as unable to transport larger molecules, penetration through the stratum corneum is the rate limiting step, physicochemical properties of drugs hinder their own transport through skin. These elastic vesicles can squeeze themselves through skin pores many times smaller than their own size and can transport larger molecules. Transfersomes are applied in a nonoccluded method to the skin, which permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. It can be applicable as drug carriers for a orbit of small molecules, peptides, proteins and herbal elements. Transfersomes can penetrate the stratum corneum and supply the nutrients, locally to maintain its functions resulting maintenance of skin.

A transfersome carrier is an artificial vesicle which resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery. Transfersome is a highly adaptable and stress-responsive, complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-

optimizing. This enables the transfersome to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency.

Advantages of Transfersomes

1. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
2. They have high entrapment efficiency, in case of lipophilic drug near to 90%.
3. This high deformability gives better penetration of intact vesicles.
4. They can act as a carrier for low as well as high molecular weight drugs, e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
5. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
6. They act as depot, releasing their contents slowly and gradually.
7. They can be used for both systemic as well as topical delivery of drug.
8. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
9. They protect the encapsulated drug from metabolic degradation.
10. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.

ETHOSOMES

Ethosomal systems are made up of soya phosphatidylcholine, ethanol and water. They may form multilamellar vesicles and have a high entrapment capacity for particles of various lipophilicities. The elastic vesicles and transfersomes have also been used as drug carriers for a range of small molecules, peptides, proteins and vaccines. Ethosome has a high deformability and entrapment efficiency and can penetrate through the skin completely and improve drug delivery through the skin. Likened to other liposomes, the physical and chemical properties of ethosomes make the legal transfer of the drug through the stratum corneum into a deeper skin layer efficiently or even into the blood circulation. This property is very important as the topical drug carrier and transdermal delivery system. Moreover, the ethosomes carrier also can provide an efficient intracellular delivery for both hydrophilic and lipophilic drugs, percutaneous absorption of matrine, an anti-inflammatory herbal drug is increased, it also permits the antibacterial peptide to penetrate into the fibrocyte easily. Ethosomes are the slight modification of well-established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.

Table 3.5: Herbal transfersomes as drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Capsaicin	Analgesic	Increase skin penetration
Vincristine	Anticancer	Increase entrapment efficiency
Colchicine	Antigout	Increase skin penetration reduction of GIT side effects
Curcuma longa	Anti-inflammatory	Better permeation

Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns (μ), ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux.

Advantages of Ethosomes

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in pharmaceutical, veterinary, cosmetic fields.
5. High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream), hence producing high patient compliance.
6. Simple method for drug delivery in comparison to iontophoresis and phonophoresis and other complicated methods.
7. The ethosomal system is passive, noninvasive and is available for immediate commercialization.

Microspheres

Microspheres are discrete spherical particles ranging in average particle size from 1 to 50 μ. Microparticulate drug delivery systems are studied and taken on as a reliable one to rescue the drug to the target site with specificity, to assert the desired concentration at the situation of interest without untoward effects. Microencapsulation is a useful method which extends the duration of drug effect significantly and improves patient compliance. Finally, the entire dose and a few adverse reactions may be thinned out since a steady plasma concentration is kept. So far, a series of active ingredients of plants, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetin, and *Cynara scolymus* extract, has been made into microspheres.

Emulsions

Emulsion refers to a nonhomogeneous dispersion system that is composed of two kinds of liquids unable to dissolve each other, and one of which disperses in the other one in a form of droplets. Broadly speaking, the emulsion is composed of the oil phase, water phase, surfactant, and subsurfactant. Its appearance is translucent to transparent liquid. Emulsion can be split up into ordinary emulsion (0.1–100 μm), microemulsion (10–100 nm), sub-microemulsion (100–600 nm), etc. Among them, the microemulsion is also called nanoemulsions, and the sub-microemulsion is also called lipid emulsion. As a drug delivery system, emulsion gets distributed *in vivo* in the targeted areas due to its affinity towards lymphatic fluids. In addition, the drug can be a sustained release in a long time because the drug is packaged in the inner phase and kept off direct touch with the body and tissue fluid. Afterward, along the oily drugs or lipophilic drugs being made into O/W or O/W/O emulsion, the oil droplets are phagocytozed by the macrophage and get a high concentration in the liver, spleen, and

Table 3.6: Herbal ethosomes

Herbal plants/constituents	Therapeutic category	Applications
Glycyrrhiza glabra	Anti-inflammatory	Increases and enhances anti-inflammatory activity
Podophyllum hexandrum	Antirheumatic and antitumor	Entrapment efficiency increases therapeutic effect
Sophora alopecuroides	Antiendotoxic and anticancer	Enhances delivery of drugs into deeper layer of skin

Table 3.7: Herbal emulsions as drug delivery systems

Herbal plants/constituents	Therapeutic category	Applications
Quercetin	Antioxidant	Enhance penetration into epidermis and stratum corneum
Silybin	Hepatoprotective	Sustained release formulations
Berberine	Anticancer	Improves absorption and residence time

kidney in which the quantity of the dissolved drug is truly heavy. While water-soluble drug is produced into W/O or W/O/W emulsion, it can be well contracted in the lymphatic system by intramuscular or subcutaneous injection. The size of the emulsion particle has an impact on its target distribution. Aside from its targeted sustained release, producing the herbal drug into emulsion will also beef up the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs' stimulus to the tissues.

CONCLUSION

Herbal medications have been widely employed all over the globe since ancient times and have been acknowledged by doctors and patients for their better therapeutic value as they cause fewer adverse effects as compared with modern medications. The drugs of Ayurvedic origin can be utilized in a more upright course with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to render the components in a new way to increase patient compliance and avoid repeated administration. This can be accomplished by designing NDDS for herbal ingredients. NDDS not only reduce the repeated administration to overcome noncompliance, but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability and so on. The novel research can also aid in capturing as well as to remain in the market. But there are many challenges with herbal drugs which need to be overcome like difficulty of conducting clinical research in herbal drugs, development of simple bioassays for biological standardization, pharmacological and toxicological evaluation methods' development, investigation of their sites of absorption, toxic herbal drugs in use, discovering various animal models for toxicity and safety evaluation, legal and regulatory aspects of herbal drugs and so on.

Unit II

Intellectual Property Rights and Patenting of Herbal Formulations

CHAPTER 4

Intellectual Property Rights

CONCEPTS OF IPR

The World Health Organization (WHO) defines traditional medicine as "the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses". "Traditional" means that the knowledge is created in a manner that reflects community traditions; it is often intergenerational and created and held collectively. "Traditional", therefore, does not necessarily mean "old" but is rather related to the way in which the knowledge is created, preserved and transmitted.

The World Intellectual Property Organization (WIPO) is primarily concerned with "protection" of traditional medical knowledge in the IP sense—protection against unauthorized use by third parties.

Intellectual Property Rights (IPRs) are used in the pharmaceutical industry. Patent, trademark, industrial design, geographical indication and copyright are other forms of IPRs (Figs 4.1 and 4.2).

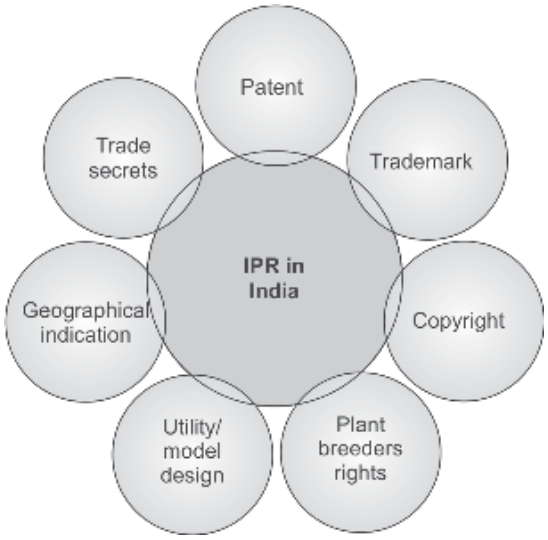


Fig. 4.1: IPR in India and its types

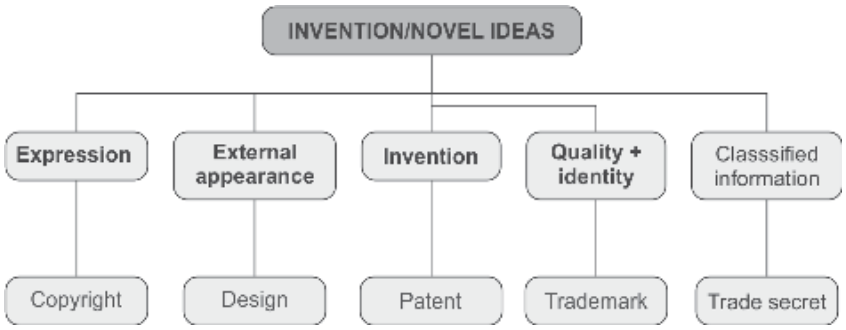


Fig.4.2: IPRs and its types

IP protection can take two forms—positive and defensive protection:

Positive protection grants IP rights over the subject matter of traditional medical knowledge. This may help communities to prevent others from gaining illegitimate access to traditional medical knowledge or using it for commercial gain without equitably sharing the benefits. It may also enable active exploitation of traditional medical knowledge by the originating community itself, for example, to build up its own enterprises based on that knowledge.	**Defensive protection** does not grant IP rights over traditional medical knowledge but aims to stop such rights from being acquired by third parties. Defensive strategies include the use of documented traditional medical knowledge to preclude, oppose or invalidate patents on claimed inventions that are directly based on such knowledge.

Grant of patent in India is governed under the Patents Act, 1970. Significant changes like provision of product patents and increase in the term of patent to twenty years were introduced in the Indian Patent Law, after India signed TRIPS (Trade Related Aspects of Intellectual Property Rights) agreement in 1995.

Intellectual property (IP) is a kind of intangible property created with the efforts of human mind or intellect. Intellectual property rights (IPRs) are the rights derived due to creation of the intellectual property. These rights are conferred upon the creator (inventor, author, etc.) of these properties. It should be noted that although the intellectual property is intangible but the material form of the intellectual property which is tangible can only be protected through IP rights. Like any other property intellectual property is also an asset, thus it can be bought, sold, mortgaged, licensed, exchanged or gifted to others. The intellectual property owners have exclusive rights over their intellectual property, which means nobody else can lawfully use the intellectual property created by them without their permission.

A trademark is a mark capable of being represented graphically and which is capable of distinguishing the goods or services of one person or enterprise from those of others. An industrial design relates to the aesthetic or outward appearance of the product. It is what makes a product attractive or appealing to customers.

A geographical indication identifies the agricultural, natural or manufactured goods, originating from a definite territory, region or locality. Copyright means the exclusive right to do or authorize to do certain acts in relation to literary, dramatic, musical or artistic work, cinematograph film and sound recording. Out of all the forms of intellectual property rights, patents are considered as most valuable assets in the pharmaceutical industry.

Terminologies Related to IPR

a. Copyright (Fig. 4.3)

Copyrights protection as obtained by the domestic law of a country and the adequacy

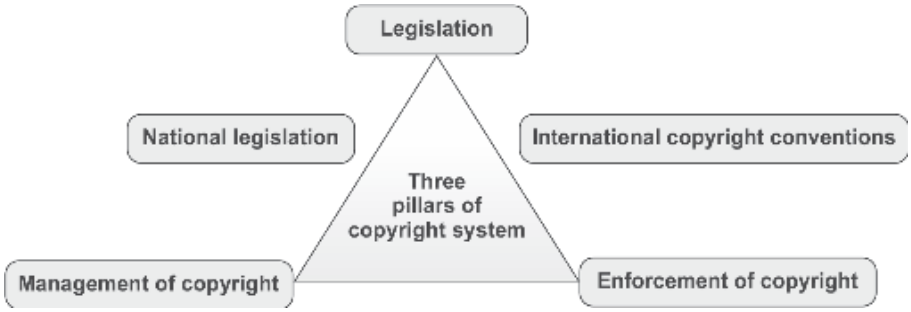


Fig. 4.3: Three pillars of copyright system

of the present Copyright Act, 1957. It is an exclusive right given by law to the creators of literacy, musical and artistic world, films and records. The creators of literacy work and artistic works such as writer, poets, composers of music and artists have rights of ownership of their works. These rights are afforded legal protection to prevent unlawful re-protection of such works.

The object of the Copyright Act is to protect the writer and the artist from unlawful re-production, plagiarism, piracy and imitation, is to promote the public good by encouraging and fostering cultural and scientific activity, to protect cultural works, the creative expression of thoughts and feelings.

The copyright enables the author to claim authorship of the work as well as to restrain or claim damages in respect of distortion or other modifications in the work or any other action which is prejudicial to his honor or reputation in relation to that work. While in case of patents, designs and trademarks, the rights can be acquired only by registration, in case of copyright registration is not necessary and it subsists automatically.

Many countries are now using copyright to protect valuable indigenous cultures, ensuring their vibrant and individual national cultural expression continues. The existence of strong and enforceable copyright laws is also a necessary precursor to participation in the global economic community, bringing particular benefits to the economies of developing countries.

b. Trademarks Law (Fig. 4.4)

A trademark is a visual representation attached to the goods for the purpose of indicating their trade origin.

Registration of his trademark gives him the exclusive right to the use of the trademark in connection with the goods in respect of which it is registered and if there is any invasion of this right by any other person using a mark which is the same or deceptively similar to his trademark, by an action for infringement in which he can obtain injunction, damages, or an account of profit made by the other person.

Functions of Trademark

- It identifies the product and its origin.
- It guarantees its established quality.

Registration for services
Renewal of 7 yrs to 10 yrs
Speedy disposal of appeals
Salient features
Increasing period of registration
Transferring of final authority to registrar
Providing enhanced punishment for the offence

Fig. 4.4: Salient features of trademark laws

- It advertises its product
- It creates an image of the products in minds of the public particular customers.

c. Geographical Indication

Certain geographical names have acquired a lot of importance in the commercial market, particularly with regard to the goods uniquely associated with such names. In respect of any agricultural goods, natural goods or manufactured goods, or any goods of handicraft or goods of industry including foodstuff, generally bears the geographical indications to attract the attention of the consumers.

Traders attach considerable value to the public recognizing the source, particularly the place of origin of the goods, especially when the name of that place is taken as a synonym necessarily after long and continuous use, for some special quality associated with the product originating from that place. Examples are Darjeeling tea, Kanjeevaram silk, etc.

There is every possibility of misusing such geographical names and wrongly applying to even those goods or products, not associated with such names. Persons producing such articles will, justifiably, claim an exclusive right to use such geographical appellations in the description of their products, which implies that they would seek to prevent traders producing those goods elsewhere.

d. Design of an IPR

A design is something which is applied to an article and is not the article itself. An article to which the design is to be applied must be something which is to be delivered to the purchaser as finished goods. The buildings and structure are not articles within the definition of design. But portable structures or models which are sold as finished articles may subject matter for registration of design.

Design right is a new intellectual property right which applies to original, non-common place designs of the shape or configuration of articles. It is not a monopoly right but a right to prevent copying and lasts until five years from the date of registration, which is extendable for a further period of five years, and for another period of five years on payment of requisite fee. A design right is a property, which like any other business commodity, may be bought, sold or licensed. All applications for registration of design are to be made to the controller of patents by a person claiming to be proprietor to the design. There are four features relevant to an industrial or product design. They are shape, configuration, pattern and ornament. The shape and configuration refer to the form of an article and is usually three dimensional in nature. Pattern and ornament are decorative features ordinarily applied to be surface of the article and they are in the nature of two dimensional. The design refers to features of shape which appeal to the eye should be judged solely by the eye and not by any functional considerations. A design in order to be registered must be both new and original and not previously published. The words 'new' or 'original' involves the idea of novelty either in the pattern, shape, or ornament itself. In deciding the question of novelty or originality evidence of experts in the trade is admissible. The design for registration should not be published previously.

Publication may be of two types:

i. Publication in prior documents, and

ii. Publication by prior use

e. Patent

Patents are granted for protection of the inventions. Patent is an exclusive right granted by the government to the applicant for an invention. A patent can be applied by the inventor or any other person/company assigned by the inventor. It is the right to exclude others from unauthorized making, using, offering to sale, selling or importing the invention. Patent is a negative right that means patent is not a right to make, use or sell the invention, rather it is a right that empowers the patentee (patent owner) to prevent or stop

the use of his/her invention by third parties without his/her permission. Patent includes right to license others for the purpose of making, using or selling the patented invention

A patent is a contract between an applicant/inventor and the government wherein the government provides right of protection of the invention for a limited period of time after the full disclosure of the invention by the applicant/inventor. Thus, patenting provides a strategy for protecting inventions without keeping the invention secret.

Patent offers technical solution to a technical problem. Patent is granted only to those inventions which satisfies certain conditions known as criteria of patentability. Patents have limited term of 20 years counted from the date of filing the patent application. Patent is a territorial right, thus it can be enforced only in the country where it is granted. Therefore, any legal action against the infringement or violation of the patent rights can be sought only in that country only. For getting patent protection in different countries patent has to be applied in each of the countries.

History of Indian Patent System

The patent system has been introduced and known in India since 19th century. The first patent act came into effect in the year 1856. It was based on British Patent Law of 1852. This act granted exclusive rights to inventors for period of 14 years. Later the patent law was amended from time to time.

Table 4.1: History of IPR

Phytosomes	Source
Year	Act
1856	The Act vi of 1856
1859	The Act modified as Act xv
1872	The Patents and Designs Protection Act
1883	The Protection of Inventions Act
1888	Consolidated as the Inventions and Designs Act
1911	The Indian Patents and Designs Act
1972	The Patents Act (Act 39 of 1970)
1999	Patents (amendment) Act, (1999) came into force from 01-01-1995.
2002	The Patents (amendment) Act 2002 came into force from 20th May 2003
2005	The Patents (amendment) Act 2005 effective from 1st January 2005

Patent cooperation treaty (PCT) provides a route to file an international patent application through with patent can be filed in a large number of countries through a single patent application. However, after filing the PCT application grant of patent remains under the discretion of the individual patent office only.

A patent is a legal monopoly granted to the owner of a new invention which is capable of use, for a limited period of time. It is a statutory privilege granted by the government to inventors and other persons deriving their rights from the inventor.

Under the concept of exclusive right, an inventor may exclude all others from the manufacture, use and sale of a qualifying

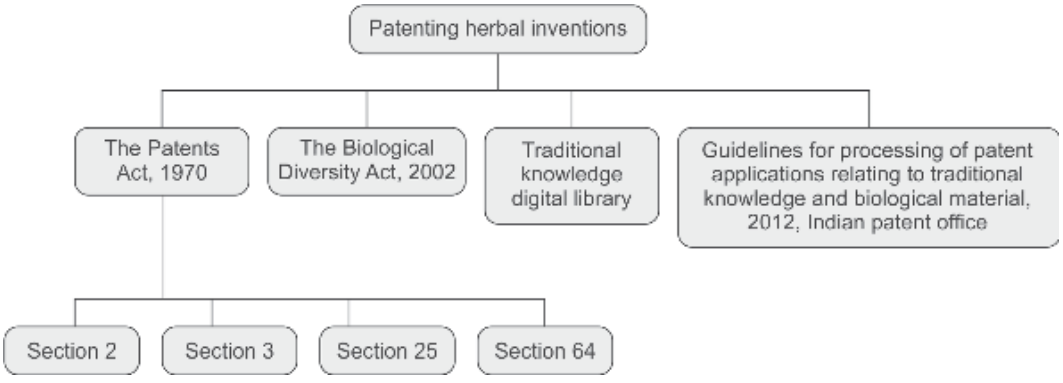

Patenting herbal inventions
The Patents Act, 1970
The Biological Diversity Act, 2002
Traditional knowledge digital library
Guidelines for processing of patent applications relating to traditional knowledge and biological material, 2012, Indian patent office
Section 2
Section 3
Section 25
Section 64

Fig. 4.5: Laws governing patenting herbal inventions

invention. With regard to the duration of the exclusive right, there is a length of time, whether fixed, adjustable, renewable or indefinite. A patent is a form of industrial or intellectual property granted in one state cannot be enforced in another state unless the invention concerned is also patented in that state. Mainly states that the concept of patent and its essential ingredients like novelty, invent step, lack of obviousness and sufficiency of description have remained the same ever since was conceived over four hundred years ago. A patent is not granted for an idea or principle as such, but for some article or the process of making some article. A patent is to encourage and develop new technology and industry. An inventor has exclusive right to keep it secretly. The patent is granted for a statutory period and after the expiry of monopoly period others can use the invention or improve upon it. Patents have assumed an international character. The international convention for the protection of Industrial Property (i.e. Paris convention) and the TRIPS Agreement of WTO provided patent rights for industrial property in all the countries of the union for the protection of industrial property. In India, the rights conferred on a patentee are purely Statutory rights conferred by the Patent Act 1970 and as amended from time to time. India has had a patent system since 1856, and the present Patent Act, 1970 is a successor to the Indian Patent and Design Act, 1911. The 1970 Act made a significant departure from the previous Act in removing the scope in the 1911 Act for obtaining product patents for drugs and medicines and certain classes of chemicals, by expressly prohibiting, through Section 5 of the Act, as it stood before the 1999 Amendment, the issue of a patent in respect of claim for the substance itself where:

i. The invention claimed that the substance was one intended for use, or capable of being used, as food or as medicine or drug, or
ii. The invention related to a substance prepared or produced by chemical processes (including alloys, optical glass, semiconductors and intermetallic compounds)

Confidential information: People in business, trade and manufacture prepare to keep the information relating to their financial management, inventive administrative procedures which contribute to efficiency in production and value addition undisclosed. The disclosure of such information might help his competitors and predators of knowledge. Secrecy and a belief in its efficiency and utility are the factors which make the information undisclosed. If the undisclosed information is already known or is in common use or ceases to be of any utility the information loses its characteristics of undisclosed or confidentiality. The right in undisclosed information is a civil right. It is inherent in every person acquire, retain and protect undisclosed information about his business, trade and manufacture.

The trade related aspects of intellectual property rights (TRIPS) of WTO protects the undisclosed information globally.

Patents (for protection of inventions): The Patents Act, 1970. Amended by Patent (Amendment) Act, 2005. The Patents Rules, 2003 as amended by The Patent (Amendment) Rules, 2005. The Intellectual Property Appellate Board (Patents Procedure) Rules, 2005. The Patents (Appeals and Applications to the Intellectual Property Appellate Board) Rules, 2011. For protection of traditional medicine, any patent being filed and using biological material, e.g. specific herbs and plants, provisions of the Biological Diversity Act, 2002 and Biological Diversity Rules, 2004 must be satisfied.

f. Curbing Anti-Competitive Licensing Contracts

The owner of a copyright, patent or other form of intellectual property right can issue a license for someone else to produce or copy the protected trademark, work, invention, design, etc. The agreement recognizes that the terms of a licensing contract could restrict competi-

tion or impede technology transfer. It says that under certain conditions, governments have the right to take action to prevent anti-competitive licensing that abuses intellectual property rights. It also says governments must be prepared to consult each other on controlling anti-competitive licensing.

g. Convention on Biodiversity (CBD)

The convention was opened at the United Nations Conference on Environment and Development in Rio de Janeiro in June 1992. It came into force at the end of 1993 and has now been ratified by the overwhelming majority of countries, for whom it is now a legally binding commitment to conserve biological diversity, to sustainably use its components and to share equitably the benefits arising from the use of genetic resources.

h. Compulsory Licensing

If the reasonable requirements of the public with respect to the patented invention have not been satisfied or if the patented invention is not available to the public at a reasonable price, then a prayer for the grant of a compulsory license to work the patented invention can be made. This is done at any time after the expiry of a three years period from the date of the grant of a patent.

i. GATT (General Agreement on Tariffs and Trade)

GATT, the organization which was established in 1947 as the organization overseeing the multilateral trade system has been replaced by WTO with effect from January 1, 1995.

j. IPC

International patent classification (IPC) subdivides the whole gamut of technology into different sub-groups and is used by the national patent offices throughout the world in classifying the subject matter contained in patent documents. Each patent document bears one or more IPC code assigned to it by the respective patent office.

k. Parallel Import

Parallel imports involve the import and resale in a country, without the consent of the patent holder, of a patented product which was put on the market of the exporting country by the title holder or in another legitimate manner.

l. TRIPS

Agreement on trade-related aspects of intellectual property rights (TRIPS 1994); this agreements constitutes Annex IC of the Marrakesh Agreement Establishing the World Trade Organization, which was concluded on April 15, 1994, and entered into force on January 1, 1995. The TRIPS Agreement binds all members of the WTO.

m. TKDL

Traditional knowledge digital library (TKDL), an Indian initiative, presently aims at documenting and classifying according to IPC, knowledge from traditional systems such as Ayurveda, Unani and Siddha.

n. TKRC

Traditional knowledge resource classification (TKRC) is the classification evolved to enable retrieval of information on traditional knowledge in a scientific manner so that it can be readily linked to IPC.

o. WIPO

World intellectual property organization (WIPO) is an international organization dedicated to promoting the use and protection of works of human intellect and is one of the sixteen specialized agencies of the United Nations System of organization. Presently, 177 nations are its members.

p. WIPONET

WIPONET is a global intellectual property network set up by WIPO enabling the integration of IP information resources, processes and systems of worldwide intellectual property communities, particularly IP offices of the member states.

q. WTO

World Trade Organization is the only global international organization dealing with the rules of trade between nations. WTO comes into being on January 1, 1995. As one of the youngest international organization, it is a successor to GATT.

IPR LAWS IN INDIA (Fig. 4.6)

As a member of the various international conventions and agreements, India is bound to enact/amend relevant domestic laws to gear up and face the challenges of globalization. In order to confirm to the stipulations in the TRIPS (Trade-*Related* Aspects of *Intellectual Property Rights*) Agreement, IPRs related laws in India are undergoing changes.

A Patent Act (1970) which was one of the most important milestones in the history of IPR laws in India amendments by government in 1999, 2002 and 2005. The main changes brought through the amendments do not substantially affect traditional knowledge, farmers' rights and biodiversity. There are also a few provisions, which attempt to reduce biopiracy. As an example, the scope of an 'invention' has been expanded to cover all grounds of new scientific creations. Despite new uses of known substances, including the duplication of traditional knowledge have been specifically excluded from patentability. In addition, the nondisclosure of the source of geographical origin of a traditionally known material has been made a basis for the challenge of a patent.

The Biological Diversity Act, 2002 was adopted following India's ratification of the biodiversity convention (CBD). It aims to conserve biodiversity, sustainable use of biological resources and equitable sharing of benefits that arise from their use or traditional knowledge. It mandates the setting up of institutions at national, state and local levels, for the purpose of regulation of biological diversity. The Act attempts to regulate access to biodiversity for commercial purposes, to fight biopiracy, and recognise community rights over traditional knowledge and biodiversity.

Plant Varieties Protection and Farmers Rights (PVPFR) Act, 2001 was enacted under the obligations set out in agreement on trade related intellectual property rights (TRIPS) which mandates the protection of plant varieties either by patents. The Indian legislation on plant varieties protection (PVP) is

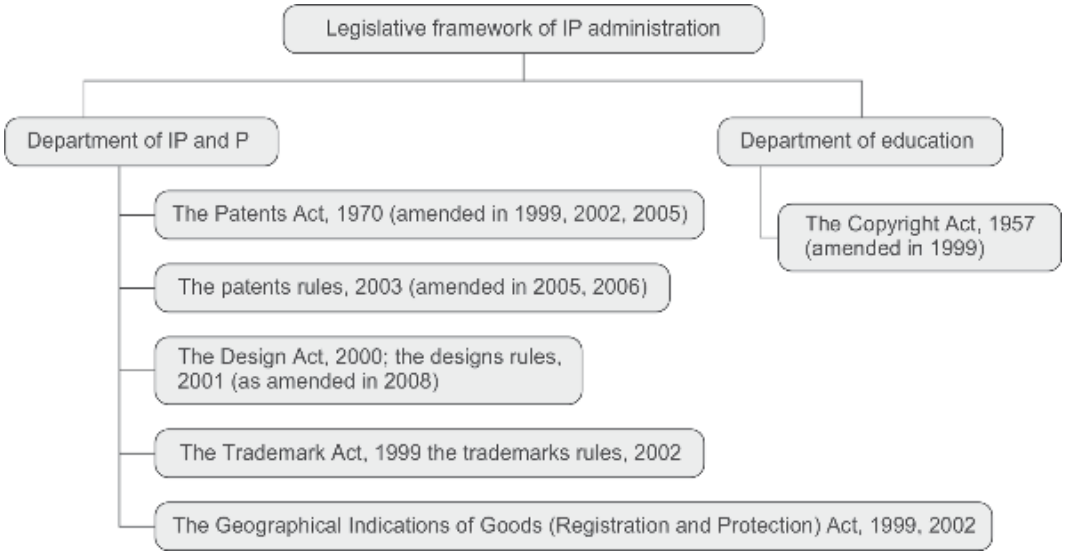

Legislative framework of IP administration
Department of IP and P
Department of education
The Patents Act, 1970 (amended in 1999, 2002, 2005)
The Copyright Act, 1957 (amended in 1999)
The patents rules, 2003 (amended in 2005, 2006)
The Design Act, 2000; the designs rules, 2001 (as amended in 2008)
The Trademark Act, 1999 the trademarks rules, 2002
The Geographical Indications of Goods (Registration and Protection) Act, 1999, 2002

Fig. 4.6: Legislative framework of IP administration

being perceived as a progressive legislation when compared to the PVP Acts adopted by the other developing nations. The PVPFR Act of India, in addition to offering protection to plant breeders in the form of plant breeder's rights, also protects the rights of the farmers to save, use, sow, re-sow, exchange, share or sell farm produce including the seeds of any unprotected variety, with an exemption to prevent the sale of branded seeds. This law incorporates some principles of the convention on biological diversity (CBD) like prior informed consent and sharing of benefits with farmers.

Development of Patent Law in India

The principal law for patenting system in India is the Patents Act, 1970. Initially, according to the provisions of this law no product patent but only process patents could be granted for inventions relating to food, drugs and chemicals. However, since 2005 product patenting is allowed in India. India being a member country of World Trade Organization (WTO) signed TRIPS (Trade Related Aspects of Intellectual Property Rights) Agreement in 1995. TRIPS prescribed the minimum standards of IP laws to be followed by each of its member countries. India being a signatory of the TRIPS agreement was under a contractual obligation to amend its Patents law to make it compliant with the provisions of the agreement. The first amendment in this series was in the form of the Patents (Amendment) Act, 1999 to give a pipeline protection till the country starts giving product patents. It laid down the provisions for filing of applications for product patents in the field of drugs and agrochemicals with effect from 1st January 1995 as mailbox applications and introduced the grant of Exclusive Marketing Rights (EMRs) on those patents. To comply with the second set of TRIPS obligations India further amended the Patents Act, 1970 by the Patents (Amendment) Act, 2002. Through this amendment provision of 20 years' uniform term of patent for all categories of invention was introduced. This amendment also made other changes in the principal act like definition of the term "invention" was made consistent with TRIPS agreement and provision for reversal of burden of proof in case of infringement suit on process patent was added in the act. The third set of amendments in the patent law was introduced as the Patents (Amendment) Act, 2005. Through this amendment product patent regime was introduced in India. Mere discovery of new form, new property or new use of a known substance was made patentable under certain conditions, provisions related to pre-grant and post-grant oppositions were modified and provision for the grant of compulsory license for export of patented pharmaceutical products in certain conditions was introduced.

Criteria of Patentability

Patents are granted to those inventions which satisfy certain conditions called criteria of patentability. According to the Indian Patent Act, a patentable invention is defined as "a new product or process involving an inventive step and capable of industrial application". Therefore, following are the basic requirements for any invention to be patentable.

a. ***Newness:*** To be patentable the subject matter of the invention must not be known before the date of patent filing. An invention is considered new if it is not published in any document or not used in the country or elsewhere in the world.

b. ***Inventive step:*** It is defined as the feature of an invention that involve technical advancement as compared to existing knowledge or having economic significance or both, that makes the invention not obvious to a person skilled in the art.

c. ***Industrial applicability:*** The invention must be capable of being made or used in an industry. For example, a new and inventive method of removing tumor cells from patient's body is industrially not applicable, thus cannot be patented.

Types of Pharmaceutical Patents in India

The Pharma industry is one of the most intense "knowledge driven" sectors. Pharmaceutical research is very costly and unpredictable in nature. Outcome of the research can be in the form of a new, inventive and useful product or process. In this highly competitive market, it is imperative for the pharmaceutical companies to protect their inventions from any unauthorized commercial use by acquiring patent rights over the invented product or process. Pharmaceutical patents in India can be classified under the following categories. This classification is based on the list of Pharma patents provided by the Indian patent office on its website.

a. ***Drug compound patents:*** These patents claim a drug compound by its chemical structure. These patent claims are usually referred as Markush type claims. A Markush claim is a claim with multiple "functionally equivalent" chemical entities allowed in one or more parts of the drug compound. Drug compound patents provide the broadest possible protection to the company's product, since other companies are not allowed to prepare such drug by any route of synthesis or produce/ sell any formulation comprising this drug before the expiry of said patent.

b. ***Formulation/composition patents:*** These patents claim a specific technology to prepare a formulation and/or quantity of its key ingredients. For example, following ayurvedic anti-retroviral composition for treatment of acquired immunodeficiency syndrome was claimed in the Indian patent no. 203986.

c. ***Synergistic combination patents:*** Drug synergy occurs when two or more drugs interact with each other in such a way that it enhances or magnifies one or more effects of those drugs. Patents can be obtained on new synergistic combinations of the drugs.

d. ***Technology patents:*** These patents are based on the techniques used to solve specific technology related problems like stabilization, taste masking, increase in the solubility, etc.

e. ***Polymorph patents:*** Polymorphs are different physical forms or crystal structure of an already known compound. Polymorphs are usually prepared to reduce impurities or increase stability of the compounds. For example, Indian patent no. 237261 claims the crystalline form B4 of atorvastatin magnesium characterized by X-ray powder diffraction pattern.

f. ***Biotechnology patents:*** Biotechnology involves the use of living organisms or biological materials in the preparation of pharmaceutical products. Biotechnology patents cover a wide range of diagnostic, therapeutic and immunological products.

g. ***Process patents:*** A process patent does not claim the product, rather it only covers a new and inventive process to produce a particular product.

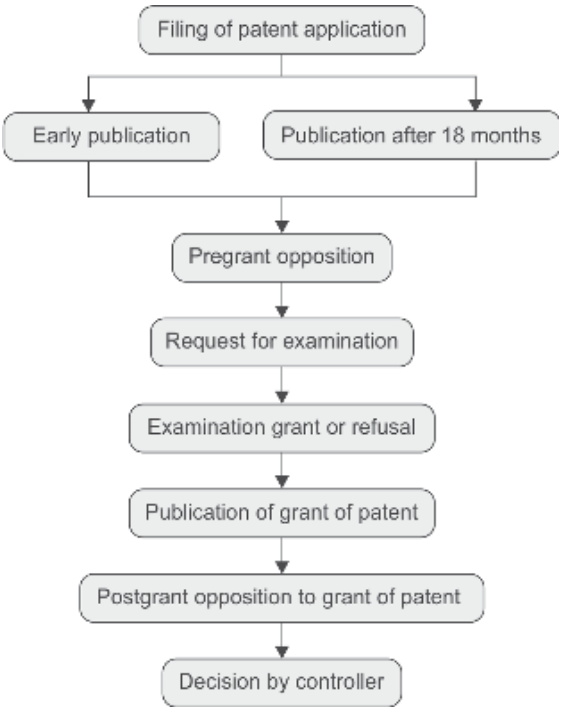


Fig. 4.7: Patent grant procedure

PROCEDURE OF PATENTING

a. Filing an application
b. Examination of application by the patent officer
c. Opposition, if any, claims to the patent
d. Granting and sealing of patent
e. Revocation of the granted patent.

FILING AN APPLICATION

a. Name, address and nationality of the applicant.
b. Title, name, address and nationality of the inventor, if he is not the applicant or co-applicant.
c. Specifications (provisional and complete) giving the details of the invention.
d. Claims, definition and scope of the invention.

EXAMINATION OF THE APPLICATION

a. Prior approved patents or applications filed
b. Novelity
c. Usefulness
d. Nature of claims

OPPOSITION

A three-month time period is given for any opposition, contrary claims can be filed and contested.

GRANTING AND SEALING OF PATENT

In case of no opposition or clearing satisfactorily all the objections by the applicant, patent is granted and sealed by the patent office by publishing in the official gazette.

REVOCATION

The validity of the patent can be challenged in high court under specified grounds. The patent will be revoked if the court upholds the challenge.

VALIDITY OF A PATENT

Patent for food and medicines and drugs produced by chemical processes. 5 years period from the date of granting the patent or 7 years period from date of filing application or whichever is earlier.

DOCUMENTATION OF PATENT

Legal Information

Form 1

- Name, address, contact details, inventor, assignee.

Form 3

- Assignments or details of foreign filling.

Technical Information

Form 2

- Background of the invention
- Summary of the invention
- Claims
- Abstract

Form 18

- Request for examination

Form 9

- Request for early publication

Form 26

- Power of authority

The intellectual property rights and the regulatory issues be looked together to harness earnings by increasing the productivity.

1. ***Herbal/food technologies:*** Research and development technological inventions by deploying different technologies have enhanced the face in the growth trends and security with the objectives and needs with foolproof strategies in the areas of agriculture or herbal plants. The innovations are not only required in organic farming but also innovation-related techniques are required at traditional plant-breeding stage, to enhance the security of herbal plants and reducing vulnerability of farmers.
2. ***Risk associated with technology:*** Synthetic biology is an emerging technology, at a nascent stage in India, which is amalgama-

Table 4.2: Similarities of IPRs and regulatory issues

Parameter	IPRs	Regulatory issues
Similarities		
1. Status	Legally enforceable	Legally enforceable
2. Controls	Government	Government
3. Financial implications	Fee involved	Fee involved
4. Purpose	Safeguard public interest by rewarding original work and thus, encouraging innovations	Safeguard public interest by rewarding original work and thus, encouraging innovations
5. Global status	Consensus on common filing procedures at regional/international level, but national rules governing grant of IPRs vary from country to country	Consensus on standards which have to be met but otherwise vary greatly from country to country. International Conferences on Harmonization (USA/ EU/ Japan)
6. Global applicability	Restricted to national level. Mechanisms for international protection still involve going through national route of each country. Regional protection mechanisms still developing	Restricted to national level. Licenses granted in particular country are applicable only in that country. Regional protection mechanisms still developing
7. Effect on trade	Regarded as barriers to international trade, since patented be copied	Regarded as barriers to products trade, since drugs being manufactured in one country may not be allowed to be sold/ manufactured in other countries, unless regulatory requirements have been met.

tion of principles of biology and engineering to facilitate "creation" and "design" microorganisms, not found in nature. This technology is to enhance the production and to help in regulatory issues. The initiatives are done mainly on biofuels but these are yet to be applied in the field of agriculture, biomedicines, etc. to get priority results to enhance the industry.

3. ***Nanotechnology:*** It is a revolutionary technology which has new potentials that are applied in the field of research and development to open new vistas in multiple disciplines ranging from health care, agriculture, cosmetics, food processing, construction, etc. to bring revolution in the regulatory framework.
4. ***Employment growth relationship:*** Analysis shows that the employment assessment has become manifest in the pharmaceutical industry which has resulted in changes in the industry during recession period. Thus the economic indicators of the country result in structural transformation leading earmarked growth in the pharmaceutical industry which ultimately constructs the economic growth in the long run and helps to harmonise intellectual property issues and regulatory issues.
5. ***Environment:*** For exploring growth, it is required that the raw materials or medicines manufactured by the Indian pharmaceutical companies to be free from "pollution heavens" so as to bring global ramification in the regulatory issues, which otherwise generally could affect global market access to the herbal plants and will ultimately have a great impact rather set back on the exports of Indian pharmaceutical industry.
6. ***Free trade agreements:*** Analysis in the sector which surrounds the pharmaceutical industry is to be explored theoretically and empirically with robust econometric estimations, especially on the part of country to

allow free trade agreements (FTA) for the growth of the economy, the industry and to propel its infrastructure worldwide.

7. ***Comprehensive economic partnership agreements:*** The economic interaction between the countries includes modalities which are crucial for trade, covering all the sensitive issues relating to formulation of rules of origin with the development angle of industry globally and also to give a push to inter-trade partnership of pharmaceutical companies of the countries for its revolutionary growth.
8. ***Expansion trade-production:*** Network is not only required within the country for promoting the growth of pharmaceutical industry but also across the borders, to build and promote its production capacities, in order to increase the trade network which will otherwise help in building long run relationship with the help of logistic services. Logistic services include stream lining the skills with knowledge and specialization and focus on research and development to avoid any barriers in the way of expansion.
9. ***Trade and investment liberalization:*** Reforms in the regulations and policies will consequently upgrade both fund and trade in the pharmaceutical industry. This will ultimately show significant rise in the productivity in different categories of pharmaceutical industry producing various medicines, which ultimately include detriments that measure the total factors for enhanced of productivity, e.g. like raw materials, quality of employment, research and development, capital, etc. It is necessary to organize and harness the goods and services, investment co-operation, research and development (R and D) cooperation and human resource development to harmonize intellectual property issues and regulations to uplift the face of pharmaceutical industry.

CONCLUSION

Numerous indigenous and local communities have protocols for protection of traditional medicine under customary law. Increasingly, a convergence is witnessed between the formal intellectual property system and 'informal' systems for protection of traditional knowledge. Their convergence results from two consequences of current globalization processes, namely the growing relevance of intellectual property to an increasing number of countries and users, and the expanding recognition that traditional medicinal know-how is a valuable economic and cultural asset within the global information society.

The India patent law is an exemplary piece of patent legislation that is aimed to balance the interests of both the common man and the inventors. After the introduction of product patent regime, a wide range of pharmaceutical products can be patented in India. Once acquired patent rights can be transferred through assignment or licensing to other persons or companies.

Unit III

Nutraceuticals and Formulation with its Origin

CHAPTER 5

Nutraceuticals—Herbal-based Formulation

DEFINITION

A nutraceutical is any substance considered as a food, or its part which, in addition to its normal nutritional value provides health benefits including the prevention of disease or promotion of health, e.g. lycopene, beta carotene.

A nutraceutical is "any non-toxic food component that has scientifically proven health benefits, including disease treatment or prevention." The term nutraceuticals were coined from "nutrition" and "pharmaceutical" by Stephen Defelice, MD, Founder and Chairman of the Foundation for Innovation in Medicine (FIM) Cranford, New Jersey, in 1989.

According to Defelice "nutraceuticals are food or part of a food that provides medical or health benefits including the prevention and/or treatment of a disease." Greek physician Hippocrates (known as Father of Medicines) said "let food be your medicine" The philosophy behind is "focus on prevention". Other words used in the context are dietary supplements, functional food, multi-functional food, etc. Functional foods are ordinary foods that have components, ingredients that incorporated into give them a specific medicinal or health benefit moreover nutritional effect.

According to Dietary Supplement, Health and Education Act (DSHEA) dietary supplements are products intended to supplement the diet that bears or contains one or more of the following dietary ingredients: A vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients. It may be taken in the form of pill capsule, tablet, or liquid form. It is not represented for use as a conventional food or as the sole item of a meal or diet. It is labeled as a "dietary supplement." Under the DSHEA (1994), the manufacturer of a dietary supple-

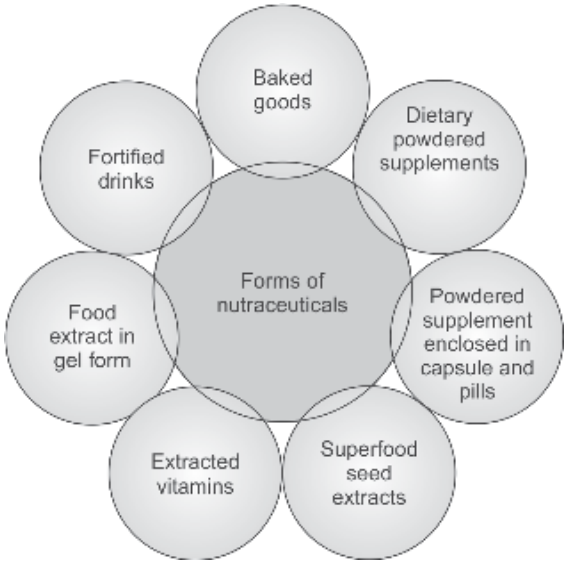


Fig. 5.1: Schematic representation of different forms of nutraceuticals

ment is responsible for ensuring that the dietary supplement is safe before it is marketed. Simply, the functional food concept can be defined as "food products" to be taken as part of the usual diet in order to have beneficial effects that go beyond basic nutritional function.

BENEFITS OF NUTRACEUTICALS

- Avoid the side effect.
- May increase the health beneficial effect.
- May have naturally dietary supplement, so do not have unpleasant side effect.
- May increase the health value, our diet and improve medical condition of human.
- May easily be available and economically affordable.

Nutritional therapy is a healing system using dietary therapeutics or nutraceuticals as a complementary therapy. This therapy is based on the belief that foods cannot only be sources of nutrients and energy but could also provide medicinal benefits.

CATEGORY OF NUTRACEUTICALS

- Substances with established nutritional functions, such as vitamins, minerals, amino acids, and fatty acids—nutrients.
- Herbs or botanical products as concentrates or extracts—herbals.
- Reagents derived from other sources (e.g. pyruvate, chondroitin sulfate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements, fortified conventional foods, and meal replacements—dietary supplements.

Dietary supplements are not intended to treat or cure disease, whereas nutraceuticals more emphasize the expected results of these products, such as prevention or treatment of diseases.

Some of the most common ways of classifying nutraceuticals can be based on food sources, mechanism of action, chemical nature, etc. The food sources used as nutraceuticals are all natural and can be categorized as:

1. Dietary fiber
2. Probiotics
3. Prebiotics
4. Polyunsaturated fatty acids
5. Antioxidant vitamins
6. Polyphenols
7. Spices

Nutraceutical can be broadly classified into the following two groups:

- Potential nutraceuticals
- Established nutraceuticals

According to nutraceutical and nutritional therapy theory, it achieves this goal by using efficacy of such nutraceuticals in detoxifying the body, avoiding vitamin and mineral deficiencies, and restoring healthy digestion and dietary habit. Phytonutrients basically are plant nutrients with particular biological activities in supporting human health.

The phytochemical work by the following way:

1. Substrate for biochemical reactions.
2. Cofactors of enzymatic reactions.
3. Inhibitors of enzymatic reactions.
4. Absorbents that bind to and eliminate undesirable constituent in the intestine.
5. Enhance the absorption and/or stability of essential nutrients.
6. Selective growth factor for beneficial bacteria.

7. Fermentation substrate for beneficial bacteria.
8. Selective inhibitors of deleterious intestinal bacteria.
9. Scavengers of reactive or toxic chemicals.

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms.

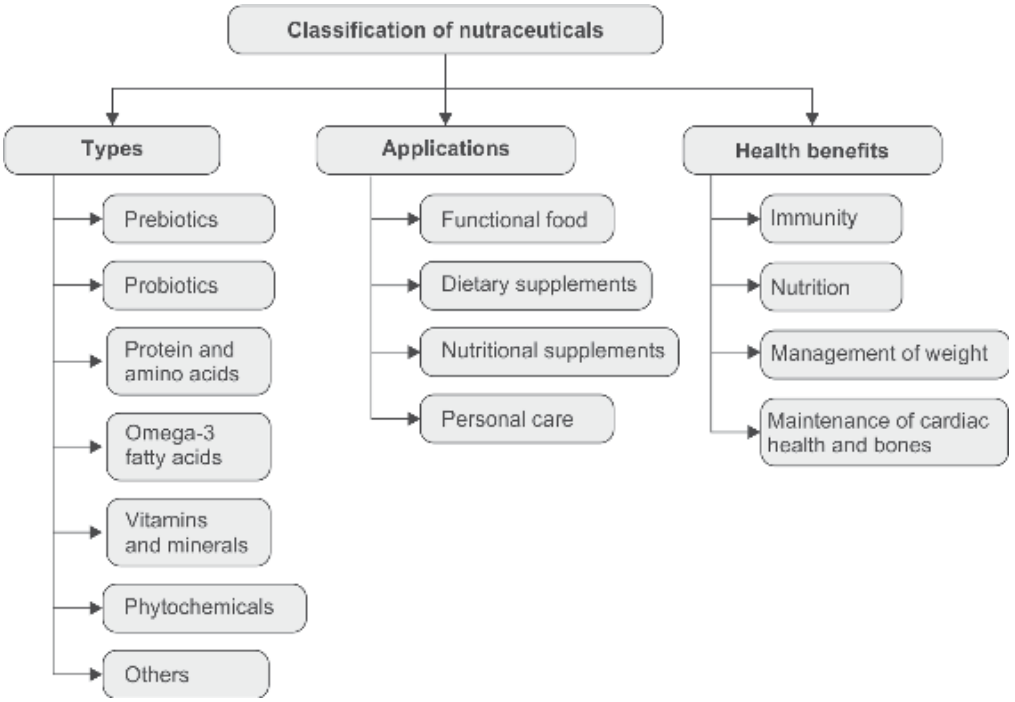


Fig. 5.2: Classification of nutraceuticals

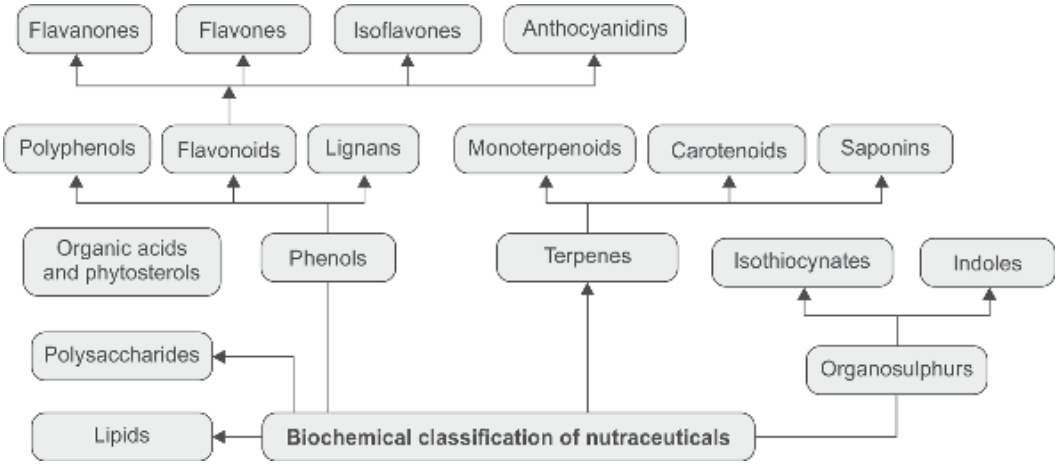


Fig. 5.3: Biochemical classification of nutraceuticals

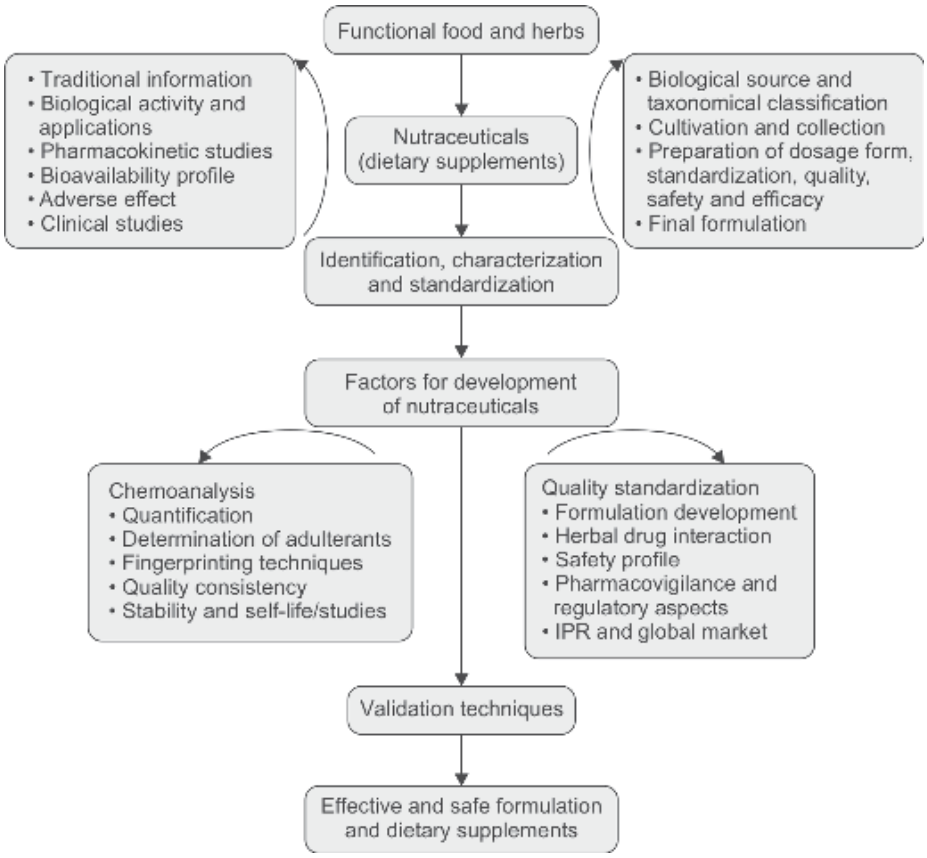


Fig. 5.4: Evaluation of herbs used in development of nutraceuticals

DEVELOPMENT AND PROCESS VALIDATION OF BOTANICALS AS FUNCTIONAL FOOD

Botanical Source

- Identity
- Scientific name (plant family, genus, species with name of authority, and if relevant, variety, and chemotype), common
- Names/local names
- Part(s) of the plant used
- Geographic origin (continent, country, region)
- Environmental conditions

Growth Conditions

- Wild or cultivated
- Good agricultural practice
- Site of collection, time of harvest, stage of growth
- Drying, fermentation
- Storage conditions
- Pre- and postharvest phytosanitary treatments (e.g. use of pesticides).

Product Classes

Vitamins: Vitamins are essential organic compounds that are not synthesized in the human or animal organism. They must be consumed with the diet either as such or as a precursor, a so-called pro-vitamin, which can be converted to the vitamin, e.g. β-carotene is a pro-vitamin that is converted biochemically to vitamin A.

Various compounds or groups of compounds have been classified as vitamins (for humans) (Table 5.2).

Vitamin E: Vitamin E is a group of compounds based on 6-chromanol. Differences between α-, β,- γ-, δ-tocopherol are given in the number of methyl groups on the chromane ring.

Table 5.1: Classes and components of phytonutrients

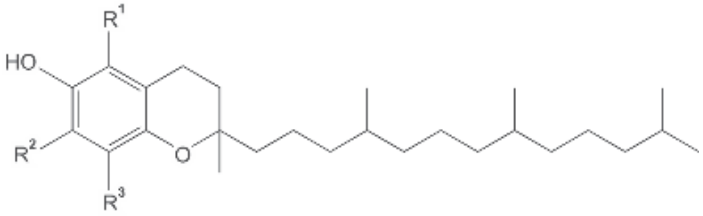
S. No.	Class/components	Sources	Potential benefits
1.	Fatty acids	Milk and meat	Improve body composition, reduce cancers
2.	**Polyphenols**		
	a. Flavonone	Citrus fruits	Neutralizes free radicals, reduce risk of cancer
	b. Flavones	Fruits, vegetables, soya bean	
	c. Catechins/tannin	Tea, babul pods	
	d. Anthocyanidine	Fruits	
	e. Pro-anthocyanidine	Cocoa, chocolate, tea, rapeseed	Reduce cardiovascular disorders
3.	Saponins	Soya beans, chickpea	Lower cholesterol, anti-cancer
4.	**Probiotics/prebiotics/synbiotics**		
	Lactobacillus	Yogurt	Improve GI health
	Fructo-oligosaccharides	Whole grains, onions	
5.	**Phytoestrogen**		
	a. Daidzein, zenistein	Soya bean, flax, maize	Reduce menopause symptoms, maintain bone health
	b. Lignans	Flax, rye, vegetables	Reduce cancer and heart diseases
6.	Carotenoids		
	β-carotene	Oat, maize fodder, carrots, vegetables and fruits	Neutralizes free radicals
	Luteine	Vegetables	Healthy vision
	Zeoxanthine	Eggs, citrus, corn	
	Lycopene	Tomatoes	Reduce prostate cancer
7.	Dietary fiber		
	Insoluble fiber	Wheat bran	Reduce breast, colon cancer
	β-glucan	Oats	Reduce cardiovascular disorders
	Whole grain	Cereal grains	

Table 5.2: Types of vitamins

Water-soluble	Fat-soluble
Vitamin B_1 (thiamin)	Vitamin A (retinols)
Vitamin B_2 (riboflavin)	Vitamin D (calciferols)
Vitamin B_6 (pyridoxal group)	Vitamin E (tocopherols)
Vitamin C (L-ascorbic acid)	Vitamin K (phylloquinone)
Pantothenic acid	
Biotin	
Folic acid	
Niacin	

Vitamin E is thought to function primarily as a chain-breaking antioxidant that prevents the propagation of free radical reactions in this manner protecting membrane lipids and blood lipids (e.g. LDL cholesterol) against oxidative damage. Vitamin E is believed to help prevent diseases associated with oxidative stress, such as cardiovascular disease, cancer, chronic inflammation, and neurologic disorders.

Vitamin K_1: Vitamin K is the term for 2-methyl-1, 4-naphthoquinone. Vitamins K are lipophilic compounds, heat resistant, stable in air, but sensitive to alkali and light. Vitamin K_1 is localized in chloroplasts of green leafy



$R^1=R^2=R^3=CH_3$: α-tocopherol
$R^2=H, R^1=R^3=CH_3$: β-tocopherol
$R^1=H, R^2=R^3=CH_3$: γ-tocopherol
$R^1=R^2=H, R^3=CH_3$: δ-tocopherol

Fig. 5.5: Vitamin E

vegetable and is also found in plant oils, e.g. from soya beans, or olives. Vitamin K has a significant role to play in human health that is beyond its well-established function in blood clotting. Vitamin K may also positively affect Ca balance, a key mineral in bone metabolism.

Folic acid: Folic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl) methyl] amino] benzoyl]-L-glutamic acid, is *de novo* synthesized in microorganisms and plants. These compounds are essential coenzymes for the C1-unit transfer at various oxidation levels.

Carotenoids: Dietary carotenoids are thought to provide health benefits by decreasing the risk of chronic diseases, particularly cancer, cardiovascular disease, and age-related eye diseases. The carotenoids are β-carotene, lycopene, lutein, and zeaxanthin.

Lutein: Lutein is one of the important and widespread natural carotenoids. Lutein can be extracted from natural sources, e.g. from tagetes, or marigold flower petals using various organic solvents.

Zeaxanthin: Zeaxanthin is found widespread in nature, e.g. as the yellow coloring in egg yolk and corn. Zeaxanthin reduces the risk of age-related macular degeneration.

Lutein and zeaxanthin are two nutritional carotenoids that are found in a wide variety of fruits and vegetables. Their antioxidant properties, their specific occurrence within the macula at high concentration has led to

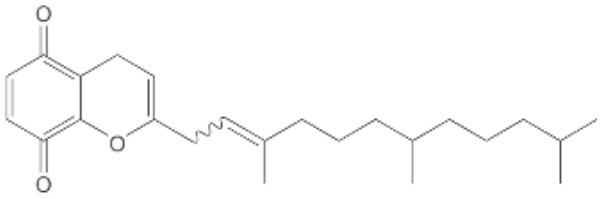


Fig. 5.6: Vitamin K_1

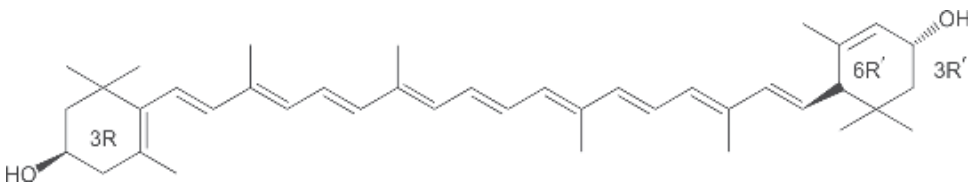


Fig. 5.7: Lutein

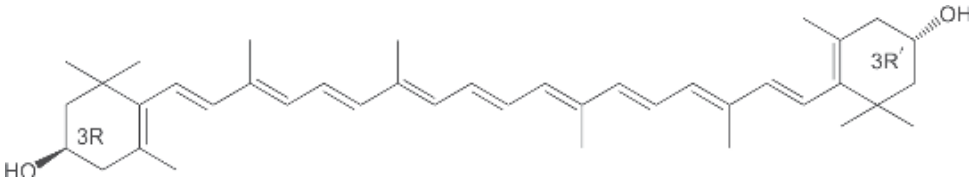


Fig. 5.8: Zeaxanthin

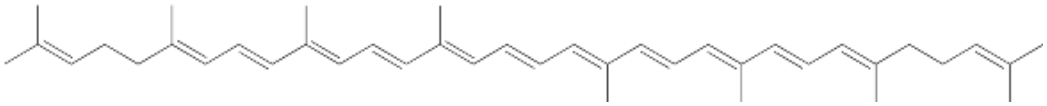


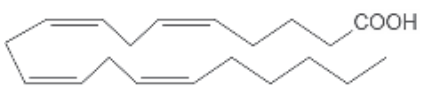
Fig. 5.9: Lycopene

expectations that the intake of these carotenoids could contribute to reducing the risk for age-related macular degeneration (AMD).

Lycopene: Lycopene (Ψ, Ψ-carotene) is the red, acyclic carotenoid highly abundant in the tomato. Besides lycopene, tomatoes also contain the carotenoid precursors phytoene and phytofluene, as well as β-carotene and some other minor carotenoids. Other dietary sources are watermelon (23–72 mg/g wet weight), pink guava (~54 mg/g wet weight), pink grapefruit (~33 mg/g wet weight), and papaya (20–53 mg/g wet weight). The high antioxidant properties of lycopene are suggested to be linked with its effect on prevention of cancer and chronic diseases, such as cardiovascular disease. Lycopene might provide protection against oxidative DNA damage suggested to be an early event in carcinogenesis.

Polyunsaturated fatty acids: Polyunsaturated fatty acids (PUFA) are of interest because of their beneficial physiological activities.

ARA: Arachidonic acid (AA), (all-Z)-5, 8, 11, 14-eicosatetraenoic acid, is an essential fatty acid and a precursor in the biosynthesis of prostaglandin, thromboxanes, and leukotrienes. AA occurs in liver, brain, glandular organs, and was isolated from liver lipids and beef.

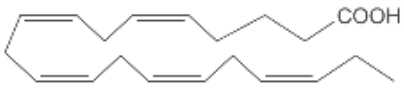


20:4ω6; 20:4n6; 20Δ5,8,11,14
arachidonic acid, AA

Fig. 5.10: Arachidonic acid

DHA/EPA: Docosahexaenoic acid (DHA) is an omega-3 PUFA. Fish oils are rich on PUFA, especially eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA). The content of EPA varies from 5 to 26% and of DHA from 6 to 26% of total fatty acid. PUFA and their ethyl esters are soluble in CO_2, and therefore, it is possible to concentrate and separate them using this nonflammable and nontoxic eluent.

20:6 ω3; 22:6n3, 22Δ4,7,10,13,16,19
docosahexaenoic acid, DHA

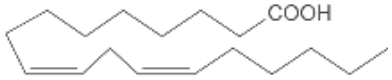


20:5 ω3; 20:5n3; 20Δ5,8,11,14,17
eicosapentaenoic acid, EPA

Fig. 5.11: DHA/EPA

CLA: Conjugated linoleic acid (CLA) was identified as a potential mutagen inhibitor. CLA is a term describing several isomers of linoleic (LL) acid.

Health effects of PUFA: There are two main classes of PUFA, the omega-6 and the omega-3 that are formed from the two essential fatty acids linoleic and α-linolenic acid, respectively. These fatty acids have a structural role in cell membranes, where they regulate fluidity and affect the function of membrane related proteins. In addition, PUFA are the precursors of eicosanoids, which have a variety of important biological activities and play a role in a number of diseases. The most relevant PUFA in cell membranes are arachidonic acid (AA) and docosahexaenoic acid (DHA), which are important structural and functional components of membranes especially in the central nervous system. Both DHA and AA make up a third of all lipids in the brain's gray matter. These fatty acids must be supplied in sufficient amounts during fetal and infant brain growth. A deficit of omega-3 PUFAs during the perinatal brain growth or the retinal development can lead to disorders of the central nervous system and to impairment of vision, which may be irreversible.

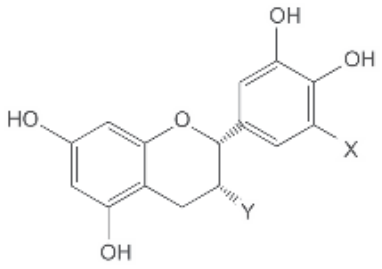


18:2ω6; 18:2n6; 18Δ9,9,12
Linolenic acid. LA

Fig. 5.12: Linolenic acid

Polyphenols: Polyphenols have been found to have beneficial health effects.

EGCG: (-)–Epigallocatechin gallate is one of the complex mixtures of polyphenols found in green tea (*Camellia sinensis*). Other catechins found in *Camellia sinensis*, are epicatechin (EC), and epicatechin gallate (ECG), and epigallocatechin (EGC). EGCG exerts a broad range of activities that include antioxidant, anti-inflammatory, antiangiogenic, antiartherogenic, antithrombotic, and anti-infectious properties. These activities are agreed upon to play an important role in fending off disease.



X=H, Y=OH, epicatechin
X=H, Y=$C_7H_5O_5$, epicatechin gallate
X=OH, Y=OH, epigallocatechin
X=OH, Y=$C_7H_5O_5$, epigallocatechin gallate

Fig. 5.13: Epicatechin

Flavonoids and isoflavonoids are natural antioxidants and are suggested as agents responsible in the diet for the prevention of coronary diseases, breast cancer, and prostate cancer. Chemically, flavonoids and isoflavonoids are derivatives of 4H-chromene. Most important is the 4-oxo-chromens, such as flavones and 3-hydroxyflavones. Another important flavone is the plant dye quercetin, 3, 5, 7, 30, 40-penthydroxy-flavone, one of the most important and widely distributed of the flavonoid family. The following show structures of flavone, 4H-chromene, chromone, 3-hydroxyflavone, and quercetin.

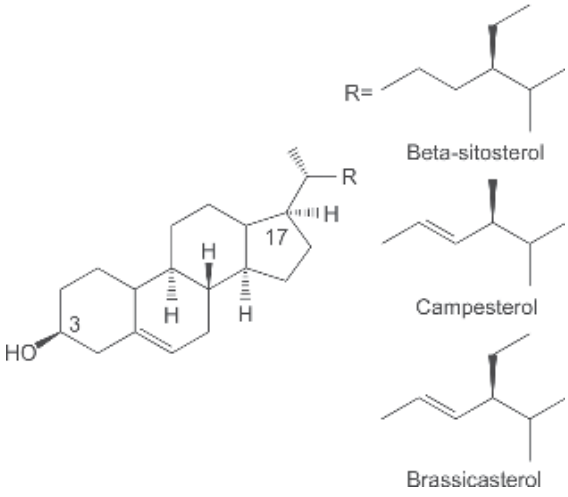
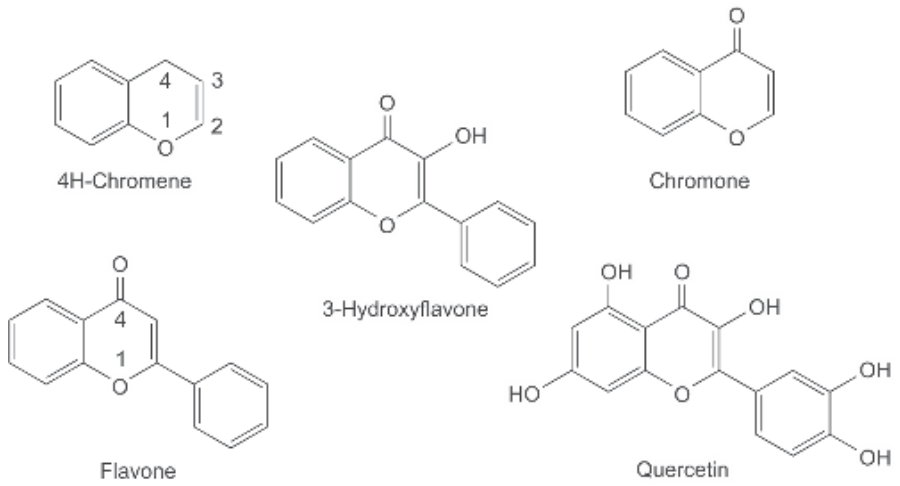


Fig. 5.14: Flavonoids and isoflavonoids

Genistein: Genistein has been associated with reduced incidence of breast and prostate cancer, cardiovascular disease, and osteoporosis.



Phytosterols: Phytosterols are derived from isoprenoid biogenesis and are ubiquitous in higher plants. Usually they are C27–29 substances with a 3-hydroxyl-steran core with C8–10 alkyl and alkenyl side chains at C-17. Various phytosterols such as brassicasterol, stigmasterol, and beta-sitosterol. Phytosterols occur mostly in intracellular organelles, where they appear to play important roles in the stabilization of membranes. They have been found in nearly all plant tissues and organs, including leaves, stems, roots, blossoms, fruits, and seeds. The common dietary phytosterols are most widely established and known for their effects on serum cholesterol. These phytosterols have been shown to competitively inhibit the normally occurring adsorption of endogenous and dietary cholesterol from the intestines. Thus they can lead to lowering of serum cholesterol levels.

Others

Creatine: Creatine is a substance that occurrs in the human body. The total amount of creatine in a normal healthy person is ~120 g (70 kg) person (256–258). Phosphocreatine, the phosphorylated creatine and creatine, are important for cellular energy storage, transport, and buffering. In the human organism, creatine is formed from the amino acids argenin, glycin, and methionin. Creatine pyruvate and its salts have several physiological property for treatment of obesity and overweight, and can be used to prevent free radicals and to enhance long-term performance.

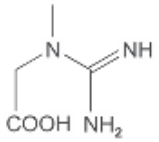


Fig. 5.15: Creatine

(R)-α-lipoic acid: Lipoic acid is a growth factor. (R)-(α)-lipoic acid is the biologically active form and racemic lipoic acid is used as an antidote for liver diseases and poisoning. L-lipoic acid serves as a coenzyme in the oxidative decarboxylation of ketoacids and can be found in every cell of vegetable and animal organisms.

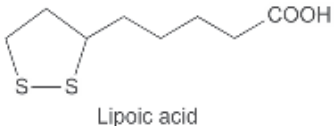


Fig. 5.16: Lipoic acid

Glucosamin: Glucosamin from exogeneous sources, e.g. food, is incorporated into the metabolic pathway of glycosaminoglycan synthesis. Glucosamin increased the production of proteoglycans and sulfate uptake by articular cartilage.

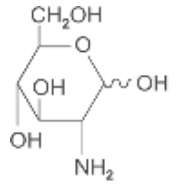


Fig. 5.17: Glucoseamine

Coenzyme Q10: Ubiquinone is a generic term for a family of quinines (2, 3-dimethoxy-5-methyl-6-polyprenyl-benzoquinone) in which the number of prenyl groups varies from 1 to 10.

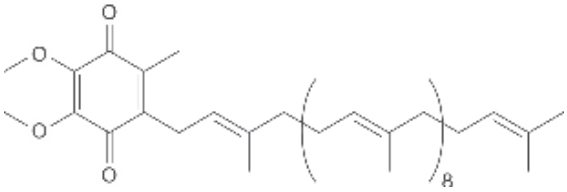


Fig. 5.18: Coenzyme Q10

NUTRACEUTICALS AND THEIR BENEFITS IN VARIOUS DISORDERS

Cardiovascular Diseases

The nutraceuticals used are antioxidants, dietary fibers, omega-3 fatty acids, vitamins, minerals for prevention and treatment of CVD. Polyphenol (in grape) prevent and control arterial diseases. Flavonoids (in onion, vegetables, grapes, red wine, apples and cherries) block the ACE and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells.

Diabetes

Lipoic acid, an antioxidant is used for treatment of diabetic neuropathy dietary fibres from psyllium have been used for glucose control in diabetic patients and to reduce lipid level in hyperlipidemia.

Ethyl esters of n-3 fatty acids may be beneficial in diabetic patients. Docosahexaenoic acid modulates insulin resistance and is also vital for neurovisual development.

Obesity

Herbal stimulants, such as ephedrine. Caffeine, chitosan and green tea help in body weight loss.

Buckwheat seed proteins acting similar to fibers present in food. 5-hydroxytryptophan and green tea extract may promote weight loss, while the former decreases appetite, the later increases the energy expenditure. A mixture of glucomannan, chitosan, fenugreek and vitamin C in dietary supplement significantly reduced body weight.

Cancer

Flavonoids which block the enzymes that produce estrogen, reduce of estrogen induced cancers. Phytoestrogens is recommended to prevent prostate/breast cancer. Soy foods are source of isoflavones, curcumin from curry and soya isoflavones possess cancer chemo preventive properties. Lycopene concentrates in the skin, testes, adrenal and prostate protects against cancer. Saponins contains antitumor and antimutagenic activities. Curcumin (diferuloylmethane) which is a polyphenol of turmeric possesses anti-carcinogenic, antioxidative and anti-inflammatory properties. Beet roots, cucumber fruits, spinach leaves, and turmeric rhizomes were reported to possess anti-tumor activity.

Treatment of Inflammation

Cucurmin which is a polyphenol of turmeric has anticarcinogenic, anti-oxidative and anti-inflammatory properties. Linoleic acid (found in green leafy vegetables, nuts, vegetable oils, i.e. evening primrose oil, blackcurrant seed oil, hemp seed oil, cyanobacteria and from spirulina) is used for treating problems with inflammation and autoimmune diseases.

Vision Improving Agents

Lutein (found in mangoes, corn, sweet potatoes, carrots, squash, tomatoes and dark leafy greens such as kale, collards and bokchoy) also known as helenien is used for the treatment

of visual disorders. Zeaxanthin (found in corn, egg yolks and green vegetables and fruits, such as broccoli, green beans, green peas, brussel sprouts, cabbage, kale, collard greens, spinach, lettuce, kiwi and honeydew) used in traditional Chinese medicine mainly for the treatment of visual disorders. Osteoarthritis: Glucosamine (GLN) and chondroitin sulphate (CS) is used for treatment of osteoarthritis. Alzheimer's disease: β-carotene, curcumin, lutein, lycopene, turmerin, etc may exert positive effects on specific diseases by neutralizing the negative effects oxidative stress mitochondrial dysfunction and various forms of neural degeneration.

Global Demand of Nutraceuticals

The nutraceutical industry lies under three main segments which include functional foods, dietary supplements, and herbal/natural products. Global nutraceutical market is estimated as USD 117 billion (INR 5148 billion). The nutraceuticals sale is projected to reach $74.7 billion at an AAGR of 9.9%. This assumes a world economic recovery in 2003 and an end to price competition.

According to a recent report, the total market for nutraceuticals in India is growing at 21 percent per annum.

As a concept, "nutraceuticals" is still in its stage of infancy in India. But it has been growing much faster than global rates at CAGR of 18% for the last 3 years driven by functional food and beverages categories. The most rapidly growing segments of the industry were dietary supplements (19.5 percent per year) and natural/herbal products (11.6 percent per year).

REGULATION OF NUTRACEUTICALS IN INDIA

Nutraceuticals has a spectacular annual growth rate of 25% in India. Nutraceuticals which contain some important component having therapeutic activity or formulated to satisfy particular dietary requirement.

FSSAI Act in 2006: Parliament passed Food Safety and Security Act. Then in 2008, FSSAI came into existence. For implementation of FSSAI Act process of prepublication consultation in 2006 has been conducted where various rules and regulation are drafted. So that by the end of September 2010 these drafted regulations will be sent for notifications.

This FSSAI Act consists of twenty-one chapters and in that the fourth article of the Act says about nutraceuticals, dietary supplements and various functional foods, and these products can be produced/manufactured, marketed, that means sold or distributed, that means import can be done by any of the company. And these products may include nutraceuticals, dietary supplements, functional food, organic food, unprocessed food, can food, novel foods, irradiated foods.

Rules which are made under the Act, that is, the substances listed in Schedules E and EI of the D and C Rules, 1945; it does not include a narcotic drug or a psychotropic substance as defined in the schedule of the narcotic drugs and Psychotropic Substances Act, 1985 and the FSSAI authority would also have to come up with the hilarious task of putting in place the various minimum levels of compliance of food laws.

The Indian Food Safety and Standard Act came into enforcement in 2006 with the following two main objectives:

- To introduce a single statute relating to food, and
- To provide for scientific development of the food processing 2009 industry.

Benefits of FSSAI

- Unification of eight laws, i.e. steps to harmonization.
- Alignment of international regulations.
- Science-based standards.
- Clarity and uniformity on novel food areas.
- Help curb corruptions.

Government Regulations: NLEA 1990

Nutrition Labeling and Education Act of 1990 (NLEA) defines how food is labeled, including nutrition labeling, in accordance with definitions established by FDA, and providing for the use of claims about the relationship between nutrients and diseases or health-related condition.

Benefits of Regulation

- Allows greater legal security and more predicable environment.
- Supports innovation (food and drink products).
- Prevents unfair competition from manufactures using false or misleading claims.

If positive claims cannot be made, the regulation does not oblige anyone to make negative claims about the product.

Registration and licensing requirements:

- A manufacturer cannot start his/her business until he/she is registered or is been licensed in a valid manner.
- The inspection of premises has been done after the issue of ID number in the way which is ordered by the act of FSSAI by the safety officer.
- Under this regulation the license which is granted shall be valid and subsisting, unless it is not specified, for a period of fifteen years.
- Manufacturers have to register with the state office commissioner and those manufacturers whose turnover is greater than 12 lakhs to have to validly get a license from FSSAI office. Even the same goes for petty food manufacturer.
- An application for the grant of a license shall be made in Form B of Schedule 2 a application should be filled so that the licence can be granted. And this license shall be issued within 60 days from the date of issue of application ID number.

Licenses: The new regulations given by FSSAI promises to simplify the licensing and registration procedure for nutraceuticals, but the areal process differs significantly. To register product in India, various licenses are needed which depends on actual product status like which requires many documents to report to the government officer by the person who imports they also need to interlink the dossiers of the product with the licensing procedures inculdes import, license for manufacture and license for marketing. Other state and national level clearances/licenses required from the regulatory side, which need to be taken care of before launching these products in India.

STUDY OF HERBS AS HEALTH FOOD

Alfalfa

Common names: Buffalo grass, chilean clover, lucernel

Biological source: *Medicago sativa* Family: Fabaceae/Leguminosae.

Part used: Leaves, stems, sprouts.

Habitat: Alfalfa is native to south-western Asia and south-eastern Europe. Also grows in North America and North Africa. Alfalfa is known as the "father of all foods" for good reason. It is loaded with important vitamins, minerals, trace minerals and protein.

Chemical constituents with mechanism of action: The leaves and sprouts contain saponins. The saponins appear to decrease serum cholesterol, but not triglycerides, by binding cholesterol and decreasing its absorption. Alfalfa seeds contain the amino acid L-canavanine. L-canavanine is metabolized to produce canaline and urea. Canaline seems to bind pyridoxine phosphate, a cofactor in the metabolism of amino acids, potentially decreasing amino acid enzyme activity. L-canavanine is thought to be responsible for the immunostimulatory effects of alfalfa. Preliminary research suggests the L-canavanine increases immune responses either by decreasing T cell regulation of B cells or by directly binding B cells. Increased activity of B cells

can lead to an increase in auto-antibody production and drug-induced lupus symptoms.

Uses

- Orally, alfalfa is used as a diuretic, for kidney conditions, bladder and prostate conditions, asthma, arthritis, rheumatoid arthritis, diabetes, indigestion, and thrombocytopenic purpura.
- It is also used orally as a source of vitamins A, C, E, and K_4; and minerals calcium, potassium, phosphorous, and iron.
- This plant also contains chlorophyll, which is good for reducing bad breath and body odour.
- This plant is commonly used for arthritis, digestive problems, as a diuretic and for reducing high cholesterol.
- It is a very inexpensive source of easily digested nutrients. Alfalfa is high in beta-carotene and builds the immune system.
- Sprouted alfalfa seeds contain saponins, which are reported to be toxic to red blood cells *in vitro*.
- However, it is harmless to human consumption and has many health beneficial properties like anti-inflammatory, immune-stimulating activity, anti-tumor activity, etc.
- Alfalfa sprouts have about 8% saponins content according to commercial sprout growers. When compared with alfalfa seeds sprouting increases the saponin content to 450%. Saponins bind with bile acids. Some large intestinal bacteria converts bile into highly carcinogenic substance where, bile that binds with saponins prevents the formation of toxin.
- Presence of saponins in alfalfa sprouts will destroy tumor causing cells particularly in lung and blood cancer it is more effective. It gives more immunity for stomach.

Caution: Pregnant and nursing women should not eat alfalfa seeds due to their content of stachydrine and homostachydrine (may promote menstruation or cause miscarriage). People in general should never eat alfalfa seeds. They contain high levels of the toxic amino acid canavanine. Alfalfa is high in vitamin K and may work as an anti-coagulant, so it should not be taken by people taking blood thinning medication.

The cost-effective nutraceutical product containing alfalfa along with other cereals and pulses would serve the humanity to fight undernourishment in an easy and economical way.

CHICORY

Biological source: *Cichorium intybus;* Family: Compositae.

Part used: Root.

Habitat: Chicory has been an esteemed medical plant ever since the Roman physician Galen called it "the friend of the liver" some 1,800 years ago.

Chemical constituents: The root contains up to 58% inulin and sesquiterpene lactones (lactucine and lactupicrine), sugar, as well as vitamins (B, C, K, P) and minerals. Chicory flowers contain cichoriin, which is 6,7-glucohydroxycoumarin. The greens contain chicoric acid (dicaffeoyl tartaric acid), flavonoids, catechol tannins, glycosides, carbohydrates, unsaturated sterols and triterpenoids and tartaric acid.

Medicinal uses

- A syrup of chicory, rhubarb and oats was given to patients with liver ailments. It was also considered valuable for treating a variety of other ailments.
- A syrup of the whole plant was prepared with sugar and taken to cure insomnia.
- The bruised fresh leaves were applied externally for healing eye inflammations and boiled in broth for strengthening the digestion of the persons with weak stomachs.
- An infusion of the leaves was also used to reduce fever in children.

- A distilled water of chicory or the juice pressed from it was good for pregnant women and especially to soothe nursing breasts that were swollen from too much milk.
- Chicory is an excellent bitter tonic for the liver and digestive tract.
- Recommended for loss of appetite and dyspepsia.
- The root is therapeutically similar to dandelion root, supporting the action of the stomach and liver and cleansing the urinary tract.
- Chicory is also taken for rheumatic conditions and gout, and as milk laxative, one particularly appropriate for children.
- An infusion of the leaves and flowers also aids the digestion.
- A decoction may alleviate gallstones and kidney stones and aid in the production of bile.
- Chicory constituents may be effective in treatment of disorders involving tachycardia, arrhythmias and fibrillation. It also has been found to significantly lower cholesterol and blood sugar levels.

GINGER

Biological source: Ginger is the rhizome of *Zingiber officinale* Rosc., a herbaceous perennial belonging to Zingiberaceae.

Habitat: It is believed to be native of south-eastern Asia.

Chemical constituents: The major constituents in ginger rhizomes are carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic compounds. Terpene components of ginger include zingiberene, 5-bisabolene, 5-farnesene, 5-sesquiphellandrene, and 5-curcumene, while phenolic compounds include gingerol, paradols, and shogaol. These gingerols (23–25%) and shogaol (18–25%) are found in higher quantity than others. Besides these, amino acids, raw fiber, ash, protein, phytosterols, vitamins (e.g. nicotinic acid and vitamin A), and minerals are also present. The aromatic constituents include zingiberene and bisabolene, while the pungent constituents are known as gingerols and shogaols. Other gingerol- or shogaol-related compounds include 6-paradol, 1-dehydrogingerdione, 6-gingerdione and 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8-gingerdiol, and 10-gingerdiol, and diarylheptanoids. The characteristic odor and flavor of ginger are due to a mixture of volatile oils like shogaols and gingerol.

Uses

- Ginger and its constituents show antioxidant activity and prevent the damage of macromolecules, caused by the free radicals/oxidative stress.
- Ginger and its constituents also show a vital role as anti-inflammatory processes. Earlier studies on *in vitro* investigations of ginger preparations and some isolated gingerol related compounds showed that anti-inflammatory effects of ginger such as inhibition of COX and inhibition of nuclear factor κB.
- Ginger also acts as antitumor via modulation of genetic pathways such as activation tumor suppressor gene, modulation of apoptosis and inhibition of VEGF. Earlier study has shown that terpenoids, constituents of ginger induce apoptosis in endometrial cancer cells through the activation of p53.
- Ginger also shows antimicrobial and other biological activities due to gingerol and paradol, shogaols and zingerone.

FENUGREEK

Biological source: *Trigonella foenum-graecum;* Family: Fabaceae/leguminosae.

Habitat: Fenugreek is indigenous to the eastern shores of the Mediterranean sea, but it is grown in India, Morocco, Egypt and England.

Chemical constituents: Fenugreek seed contains 45–60% carbohydrates, mainly mucilaginous fiber (galactomannans); 20–30% proteins high in lysine and tryptophan; 5–10% fixed oils (lipids); pyridine-type alkaloids, mainly trigonelline (0.2–0.36%), choline (0.5%), gentianine, and carpaine; the flavonoids apigenin, luteolin, orientin, quercetin, vitexin, and isovitexin; free amino acids, such as 4-hydroxyisoleucine (0.09%); arginine, histidine, and lysine; calcium and iron; saponins (0.6–1.7%); glycosides yielding steroidal sapogenins on hydrolysis (diosgenin, yamogenin, tigogenin, neotigogenin); cholesterol and sitosterol; vitamins A, B_1, C, and nicotinic acid; and 0.015% volatile oils (n-alkanes and sesquiterpenes), which are thought to account for many of its presumed therapeutic effects.

Mechanism of action: The applicable part of fenugreek is the seed. The active constituents include trigonelline, 4-hydroxyisoleucine, and sotolon. Fenugreek seeds have a distinctive bitter taste and odor. Sotolon is frequently used as a flavoring for artificial maple syrup. Soaking fenugreek seeds overnight and washing the seeds in water can decrease some of the taste and odor. Fenugreek seeds contain about 50% dietary fiber and pectin and may affect gastrointestinal transit, slowing glucose absorption. About 80% of the total content of free amino acids in the seeds is present as 4-hydroxyisoleucine, which appears to directly stimulate insulin. This effect is glucose dependent and only occurs in the presence of moderate to high glucose concentrations. Some evidence suggests the seed consumption might decrease calcium oxalate deposition in the kidneys. Fenugreek contains coumarins and other constituents that might affect platelet aggregation, but this might not be significant clinically.

Uses

- Orally, fenugreek is used for lowering blood glucose in people with diabetes, loss of appetite, dyspepsia, gastritis, constipation, atherosclerosis, high serum cholesterol and triglycerides, and for promoting lactation.
- Fenugreek is used orally for kidney ailments, beriberi, hernia, impotence, and other male problems. Fenugreek is also used orally for fever, mouth ulcers, boils, bronchitis, cellulitis, tuberculosis, chronic coughs, chapped lips, baldness, and cancer.
- Topically, fenugreek is used as a poultice for local inflammation, myalgia, lymphadenitis, gout, wounds, leg ulcers, and eczema.
- In foods, fenugreek is included as an ingredient in spice blends. It is also used as a flavoring agent in imitation maple syrup, foods, beverages, and tobacco. In manufacturing, fenugreek extracts are used in soaps and cosmetics.

GARLIC

Biological source: Garlic, *Allium sativum* L. is a member of the Alliaceae family, has been widely recognized as a valuable spice and a popular remedy for various ailments and physiological disorders.

Habitat: Cultivated practically throughout the world, garlic appears to have originated in central Asia and then spread to China, the Near East, and the Mediterranean region before moving west to central and southern Europe, Northern Africa (Egypt) and Mexico.

Chemical constituents: Garlic contains at least 33 sulfur compounds, several enzymes, 17 amino acids, and minerals such as selenium. It contains a higher concentration of sulfur compounds than any other allium species. The sulfur compounds are responsible both for garlic's pungent odor and many of its medicinal effects. Dried, powdered garlic contains approximately 1% alliin (S-allyl cysteine sulfoxide). One of the most biologically active compounds, allicin (diallyl thiosulfinate or diallyl disulfide) does not exist in garlic until it is crushed or cut; injury to the garlic bulb activates the enzyme allinase, which metabolizes alliin to allicin. Sulfur

compounds: Alliin, allicin, ajoene, allylpropyl disulfide, diallyl trisulfide, sallylcysteine, vinyldithiines, S-allylmercaptocystein, and others. Enzymes: Allinase, peroxidases, myrosinase, and others. Amino acids and their glycosides: Arginine and others. Selenium, germanium, tellurium and other trace minerals.

Role of garlic in various diseases

- Garlic has demonstrated effects on several risk factors for atherosclerotic disease—hyperlipidemia, hypertension, and platelet aggregation.
- Fresh garlic, garlic powder, aged garlic and garlic oil have demonstrated antiplatelet/anticoagulant effects by interfering with cyclo-oxygenase mediated thromboxane synthesis. Garlic, *Allium sativum* L has been used for centuries in many societies against parasitic, fungal, bacterial and viral infections.
- Garlic has been proven effective as a hypolipidemic, antimicrobial, antihypertensive, hepatoprotective, and insecticidal agent in various human and animal therapies. The use of garlic extracts reduces serum cholesterol levels and increases blood coagulation time. In aquacultural operations, garlic promotes growth, enhances immunity, stimulates appetite, and strengthens the control of bacterial and fungal pathogens.
- Garlic as a natural antibiotic is one of the most effective natural immunostimulants.
- Garlic has antioxidant properties and also has beneficial effects on the cardiovascular and immune systems.
- Generally, garlic takes effect by facilitates the function of phagocytic cells and increases their bactericidal activities.
- Garlic is effective in treating intestinal parasites has been known for a long time. An extract of garlic was effective against a host of protozoa such as *Opalina ranarum*, *Opalina dimidicita*, *Balantidium entozoon*, *Entamoeba histolytica*, *Trypanosoma, Leishmania*, *Leptomonas,* and *Crithidia*.
- It has been proved that garlic has immunomodulatory properties and is well capable of enhancing protection against pathogens. Hence, it can be concluded that garlic supplemented diets in fish enhance growth rate and improves the immune response in aquaculture. Garlic can also be used as an alternative to antibiotics or chemotherapeutic agents.

HONEY

Honey is a sweet food made by bees using nectar from flowers. Honey bees transform nectar into honey by a process of regurgitation and evaporation. They store it as a primary food source in wax honeycombs inside the beehive. Honey gets its sweetness from the monosaccharide's, fructose, and glucose, and has approximately the same relative sweetness as that of granulated sugar.

Habitat: The honey bees are tropical climates and heavily forested areas. Honey bees can thrive in natural or domesticated environments, though they prefer to live in gardens, woodlands, orchards, meadows and other areas.

Chemical composition: The composition of honey includes sugars such as glucose and fructose and also minerals such as magnesium, potassium, calcium, sodium chlorine, sulphur, iron and phosphate. Depending on the quality of the nectar and pollen, the vitamins contained in honey are B_1, B_2, C, B_6, B_5 and B_3. The pH of honey is commonly between 3.2 and 4.5. This relatively acidic pH level prevents the growth of many bacteria. Honey is primarily a saturated mixture of two monosaccharides. This mixture has a low water activity.

Uses

- It has attractive chemical properties for baking, and a distinctive flavor that leads some people to prefer it over sugar and other sweeteners.
- Honey has a long history of human consumption, and is used in various foods and beverages as a sweetener and flavoring.

- It also has a role in religion and symbolism. Flavors of honey vary based on the nectar source, and various types and grades of honey are available. It is also used in various medicinal traditions to treat ailments.
- Honey have antibacterial effects, attributed to its high osmolarity, low pH, hydrogen peroxide content and content of other, uncharacterized compounds. The low water activity of honey is inhibitory to the growth of the majority of bacteria, many yeasts and moulds.
- When applied topically to wounds, osmosis would be expected to draw water from the wound into the honey, helping to dry the infected tissue and reduce bacterial growth. Even when diluted with water absorbed from wounds, honeys would be likely to retain a water activity sufficiently low to inhibit growth of most bacteria.

AMLA

Biological source: The fruit, also known as Indian gooseberry (*Emblica officinalis* gaertn.), is acclaimed for its unique nutritional and rejuvenating properties. It is consumed as a fresh fruit or in the form of food products like preserve.

Amla is a medium-sized deciduous tree with gray bark and reddish wood which successfully grows in variable agro-climatic and soil conditions. The tree grows to a height of 60 ft (18 m). The leaves are very fine and small, 3 mm wide and 1.25–2 cm long. The flowers are small, greenish-yellow and borne in compact clusters in the axils of the lower leaves. The fruits are round or oval, with smooth textured skin. There are ~6 to 8 pale visible lines, appearing as ridges. unripe fruits are light green turning yellow to red at maturity. The stone is tightly set in the center of the flesh and contains 6 small seeds.

Habitat: Indian gooseberry has been used as a valuable ingredient of various medicines in India and Middle East.

Chemical composition: It contains tannins, alkaloids and phenols. Fruits have 28% of the total tannins distributed in the whole plant. The fruit contains two hydrolysable tannins Emblicanin A and B, which have antioxidant properties; one on hydrolysis gives gallic acid, ellagic acid. The fruit also contains phyllemblin, gallic acid, corilagin, furosin and geraniin. Flavonoids like quercetin, alkaloids like phyllantine and phyllantidine are found. Along with these, it primarily contains amino acids and carbohydrates, its fruit juice contains the highest concentration of vitamin C.

Uses: Amla has been considered the best of the Ayurvedic rejuvenative herbs, because it is tridosaghna. Uniquely, it has a natural balance of tastes (sweet, sour, pungent, bitter and astringent) all in one fruit, it stimulates the brain to rebalance the three main components of all physiological functions, the water, fire, and air elements within the body.

The fresh juice of the round, acidulous fruit is used in combination with that of other myrobalans-chebulic (*Terminalia chebula*) and beleric (*Terminalia belerica*) in the form of a decoction known as triphala (three fruits). It is used as a cooling and refrigerant sherbet, and as an astringent medicine in diarrhoea, haemoptysis (spitting blood), haematemesis (vomiting blood) and other similar conditions.

GINSENG

Ginseng, the root of *Panax species*, is a well-known folk medicine. It has been used as traditional herbal medicine in China, Korea and Japan for thousands of years and today is a popular and worldwide used natural medicine.

Habitat: *Panax ginseng* belongs to the Araliaceae family and is found throughout East Asia and Russia. It grows natively in remote forests of Manchuria and North Korea, but has become over-harvested in other parts of Asia. It is cultivated in Korea, China, and Japan for export and use as a medicinal herb.

Chemical constituents: The active ingredients of ginseng are ginsenosides which are also called ginseng saponins. *Panax ginseng* contains triterpene glycosides, or saponins, commonly referred to as ginsenosides. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides, and vitamins B_1 and B_2.

Uses

- Ginseng had been used primarily as a tonic to invigorate week bodies and help the restoration of homeostasis.
- It has beneficial effects in a wide range of pathological conditions such as cardiovascular diseases, cancer, immune deficiency and hepatotoxicity.
- Ginseng products are usually used as general tonic and adaptogen to help the body to resist the adverse influences of a wide range of physical, chemical and biological factors and to restore homeostasis.
- These tonic and adaptogenic effects of ginseng are believed to enhance physical performance (including sexual function) and general vitality in healthy individuals, to increase the body's ability to fight stress in stressful circumstances and to support resistance to diseases by strengthening normal body function as well as to reduce the detrimental effects of the aging processes.

ASHWAGANDHA

Ashwagandha (*Withania somnifera*), also known as Indian ginseng, and as Indian Winter Cherry is an important ancient plant, the roots of which have been employed in Indian traditional systems of medicine, Ayurveda and Unani.

Habitat: Cultivated throughout drier parts of India.

Chemical constituents: It contains constituents like cuseohygrine, anahygrine, tropine, and anaferine, glycosides, withanolide with starches and amino acid. Withanolide consists of steroidal molecules which is said to fight inflammation. Ashwagandha stimulates the immune system, combats inflammation, increases memory, and helps maintain general health and wellness. Ashwagandha is known to increase the production of bone marrow, semen, and acts anti-aging.

Uses: Ashwgandha has long been considered as an excellent rejuvenator, a general health tonic and a cure for a number of health complaints.

It is a sedative, diuretic, anti-inflammatory and for increasing energy, endurance, and acts as an adaptogen that exerts a strong immunostimulatory and an anti-stress agent.

Ashwagandha is taken for treating cold and coughs, ulcers, emaciation, diabetes, conjunctivitis, epilepsy, insomnia, senile dementia, leprosy, Parkinson's disease, nervous disorders, rheumatism, arthritis, intestinal infections, bronchitis, asthma, impotence and a suppressant in HIV/AIDS patients.

Ashwagandha is considered to be one of the best rejuvenating agents in Ayurveda. Its roots, seeds and leaves are used in Ayurvedic and Unani medicines. Ashwagandha root drug finds an important place in treatment of rheumatic pain, inflammation of joints, nervous disorders and epilepsy. Dried roots are used as tonic for hiccup, cold, cough, female disorders, as a sedative, in care of senile debility, ulcers, etc. Leaves are applied for carbuncles, inflammation and swellings. Leaf juice is useful in conjunctivitis. Bark decoction is taken for asthma and applied locally to bed sores. Ashwagandha and its extracts are used in preparation of herbal tea, powders, tablets and syrups. Ashwagandha has anti-inflammatory, antitumor, anti-stress, antioxidant, mind-boosting, immune-enhancing, and rejuvenating properties.

SPIRULINA

Spirulina the nutraceutical food has become widely available as a food ingredient. Spirulina is the most nutritious, concentrated

food known to man containing antioxidants, phytonutrients, essential fatty acids, probiotics, and nutraceuticals. Spirulina is the best whole food source of protein, beta-carotene, gamma linolenic acid, B-vitamins, minerals, chlorophyll, sulpholipids, glycolipids, superoxide dismutase, phycocyanin, enzymes.

Spirulina contains its own antioxidants like beta-carotene, superoxide dismutase, selenium and vitamin E. Antioxidants help to protect the body against free radicals formed due to stress, exposure to toxic chemicals, drugs and poor diets. Free radicals can lead to degenerative disease like cancer, aging, age related macular degeneration, etc. Spirulina is being used as a therapeutic agent because of its antioxidant, anticancer properties and its ability to strengthen the immune system. Spirulina is known to improve malnourishment, and vit. spirulina is a good probiotic. Probiotics are good for health as they strengthen the immune system to prevent disease and cancer. Spirulina's probiotic effect helps in maintaining healthy microflora, thus helps in better digestion, absorption and protection from infection. Scientific studies also have indicated that spirulina has got anti-inflammatory, antiallergic, antimicrobial and anti-stress properties and also helps in the treatments of asthma, arthritis, etc.

LIST OF PLANT OR BOTANICAL INGREDIENTS RECOMMENDED AS NUTRACEUTICALS (WHO)

Carica papaya
Common name:
Papita
Part used:
Fruit
Dose: 50–100 gm
Carum carvi
Common name:
Syaha Jeera
Part used:
Fruit
Dose: 1–3 gm
Cassia fistula
Common name:
Amaltas
Part used:
Fruit
Dose: 10–20 gm
Centella asiatica
Common name:
Brahmi
Part used:
Leaf
Dose: 20–30 gm
Chlorophytum borivilianum
Common name:
Musali
Dose: 5–10 gm
Cicer arietinum
Common name:
Chana
Part used:
Leaf and Seed
Dose: 30–50 gm
20–30 gm
Cinnamonum zeylanicum
Common name:
Dalchini
Part used:
Stem bark
Dose: 1–2 gm
Citrullus lanatus
Common name:
Tarbuj
Part used:
Fruit, seed and oil
Dose: 50–100 gm
3–6 gm, 1–3 ml
Citrus aurantifolia
Common name:
Nimbu
Part used:
Fruit
Dose: 3–5 ml
Citrus sinensis
Common name:
Mousami
Part used:
Fruit
Dose: 50–100 ml
Cocos nucifera
Common name:
Nariyal
Part used:
Endosperm, water
and flower
Dose: 10–20 gm,
100–200 ml 5–10 gm
Crocus sativus
Common name:
Kesar
Part used:
Style and stigma
Dose: 25–50 gm
Not recommended
below 16 years

Cucumis sativus
Common name: Khira
Part used: Seed and fruit
Dose: 3–6 gm; 50–100 gm
Curcuma longa
Common name: Haldi
Part used: Rhizome
Dose: 2–5 gm
Elettaria cardamomum
Common name: Choti elaichi
Part used: Seed
Dose: 250–500 mg
Emblica officinalis
Common name: Amla
Part used: Fruit
Dose: 20–30 gm
Euryale ferox
Common name: Makhana
Part used: Seed
Dose: 20–30 gm
Ficus carica
Common name: Anjeer
Part used: Fruit/leaf
Dose: 20–30 gm
Foeniculum vulgare
Common name: Sounf
Part used: Fruit
Dose: 5–10 gm
Glycine max
Common name: Soya bean
Part used: Seed
Dose: 20–40 gm
Lithci chinensis
Common name: Litchi
Part used: Fruit
Dose: 50–100 gm
Mangifera indica
Common name: Aam
Part used: Fruit, seed and Leaf
Dose: 50–150 gm 1–2 gm; 3–5 gm
Mentha piperita
Common name: Peppermint
Part used: Leaf
Dose: 10–30 mg
Musa paradisiaca
Common name: Kela
Part used: Flower, fruit
Dose: 20–30 gm; 100–200 gm

CONCLUSION

Nutraceuticals play an important role in therapeutic development but their future will be assured by level of purity, safety and efficacy. Nutraceuticals will continue to appeal because they are convenient for today's lifestyle.

It is well documented in literature that lack of nutraceuticals on our everyday diet leads to various diseases. The present age is facing stress, pollution, hyperactivity and tension, where nutraceuticals play beneficial role in prevention and cure of the diseases. Nutraceuticals have proven health benefits and their consumption. It will keep diseases at bay and allow humans to maintain an overall good health. Although nutraceuticals have significant promise in the promotion of human health and disease prevention, health professional, nutritionists, and regulatory toxicologist should strategically work together to plan appropriate regulation to provide the ultimate health and therapeutic benefit to mankind. Herbal nutraceutical is a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity, and quality of life.

Unit IV

Herbal Cosmetics and Formulation with its Origin

CHAPTER 6

Cosmeceuticals—Herbal-based Cosmetic Preparation

DEFINITION

The word cosmetic was derived from the Greek word "*kosm tikos*" meaning having the power, arrange, skill in decorating.

The term ***Cosmeceuticals*** was first used by Raymond Reed founding member of US Society of Cosmetics Chemist in 1961 to brief the active and science-based cosmetics. The above term was further used by Dr Albert Kligman, 1984 to refer the substances that have both cosmetic and therapeutic benefits. According to the FDC Act, United States, 1938, a cosmetic is defined as an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting structure or function.

Examples skin moisturizers, perfumes, lipsticks, fingernail polishes, eye, and facial makeup preparations, shampoos, permanent waves, hair colors, toothpastes, and deodorants, as well as any material intended for use as a component of a cosmetic product. These cosmeceuticals, serving as a bridge between personal care products and pharmaceuticals, have been developed specifically for their medicinal and cosmetic benefits.

Cosmeceuticals refers to the mixture of cosmetics and pharmaceuticals. The term cosmeceuticals refer to the substances that are used in both cosmetic and therapeutic benefits.

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. A cosmeceutical is an ingredient with medicinal properties that manifests beneficial topical actions and provides protection against degenerative skin conditions. It encompasses cosmetic actives with therapeutic, disease-fighting, or healing properties, thereby serving as a bridge between personal care products and pharmaceuticals.

The classification of herbal cosmetics as per dosage form and as per related parts is shown in Figs 6.1 and 6.2.

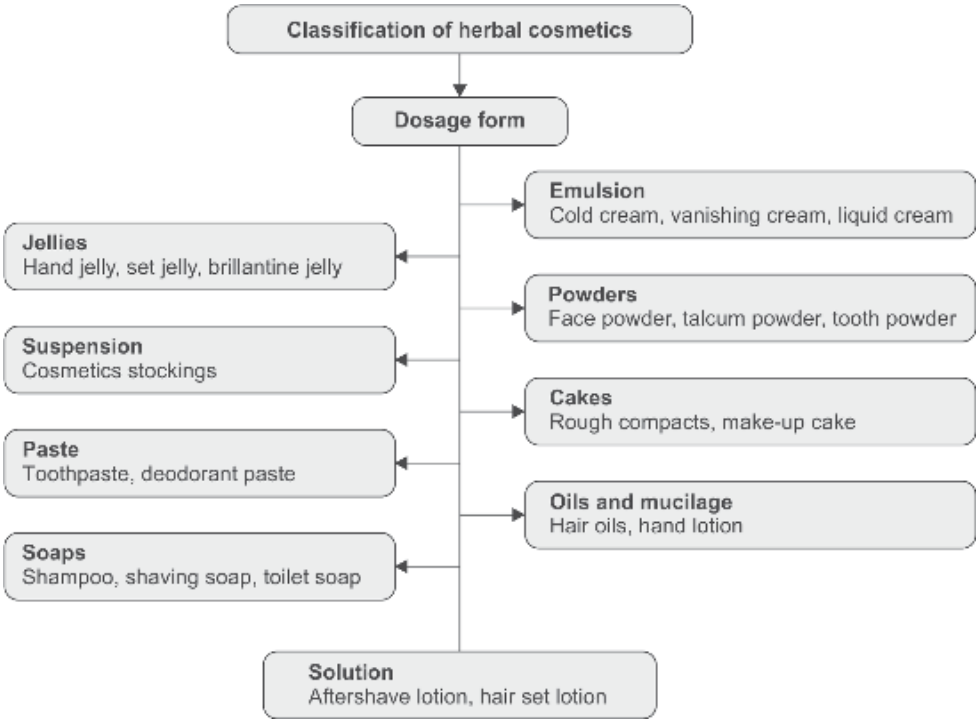


Fig. 6.1: Classification of herbal cosmetics

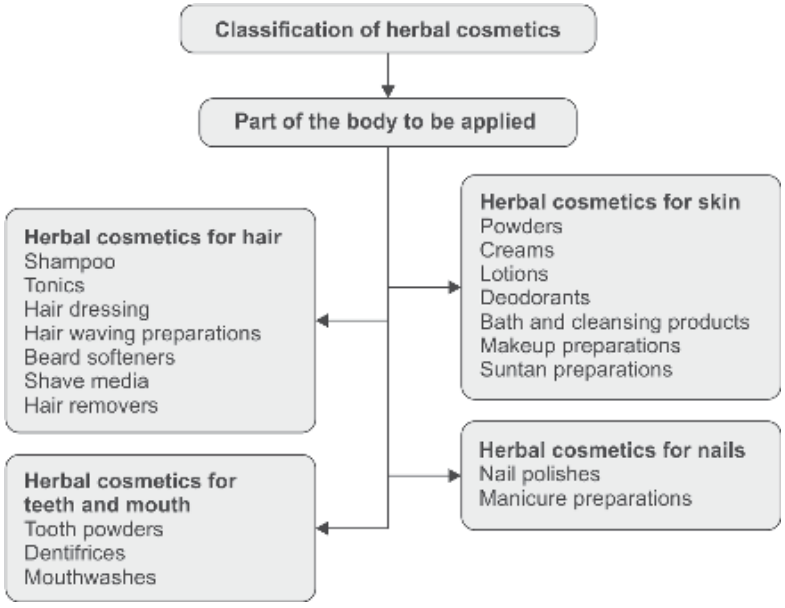


Fig. 6.2: Classification of herbal cosmetics as per applied parts

Unit IV

Cosmeceuticals are the development made within the world of dermatological products and the new beckon in skin care. Cosmeceuticals are topical cosmetic pharmaceutical hybrids intended to enhance the health and beauty of skin. Cosmeceuticals products are

those poised on the gap between cosmetic products that simply cleanse and beautify, and pharmaceuticals that cure and heal.

THE STRUCTURE OF THE SKIN

Macroscopic Characteristics

The skin is the largest, most extensive organ of our body. In fact, the average adult has about 170–200 cm^2 of skin with a weight that varies between 15 kg and 17 kg (obviously varying according to the subject's height and dimensions). The thickness of the epidermis, the outermost layer of the skin, can be from 0.5 mm in the thinnest areas (the eyelids, for example) to 4–6 mm at its thickest points (as on the palm of the hand and the sole of the foot). This thickness parameter becomes especially important when a substance is applied to the skin, be it a pharmaceutical or cosmetic product. In fact, once in contact with the skin any substance can penetrate the cutaneous barrier in a way directly proportional to the skin's thickness at that point. The skin tissue houses within its structure other important constituents: Hairs, nails, etc. (the skin's annexes). The whole of the skin is covered with hairs. In some areas the hairs are more developed and more coloured, as on the scalp, in the pubic region, and in the armpit. In other areas they are finer and much paler. These characteristics vary above all according to sex but also with individual biology. Tiny, invisible openings are found over the entire skin surface. These are the outlets of the eccrine sudoriparous glands, which, together with the apocrine sudoriparous glands and the sebaceous glands.

Microscopic Characteristics (Fig. 6.3)

Epidermis: The most external layer in contact with the environment.

Dermis: Below the epidermis it is the structural component of the skin and the underlying organs.

Hypodermis: Immediately below the dermis, composed of a layer of adipose cells and representing a "cushion" of fat between the skin and the organs underneath.

The epidermis: The epidermis is composed of different types of cells that overlap, not randomly but in a well-defined manner. There are four different cell types:

1. Keratinocytes
2. Melanocytes
3. Langerhans cells
4. Merkel cells

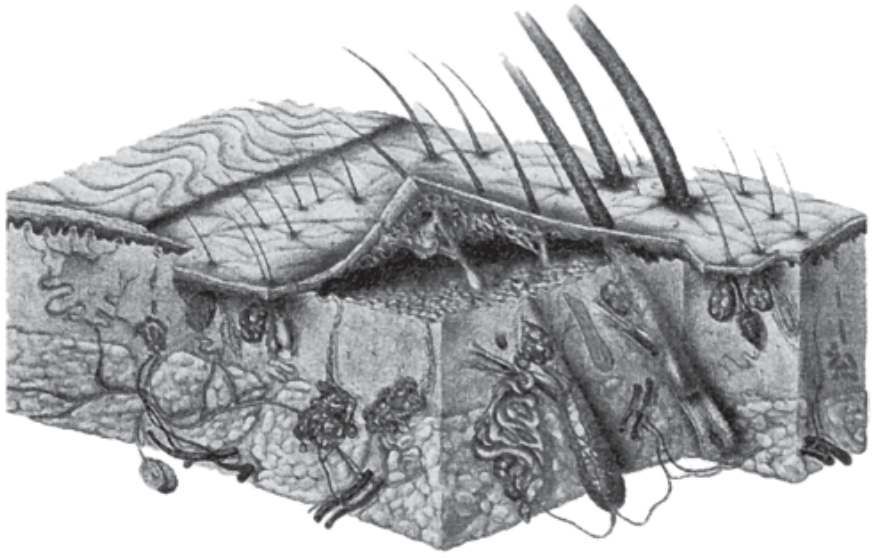


Fig. 6.3: Diagram of a skin section

The keratinocytes: The "keratinocytes" are the predominant cell type and owe their name to the characteristic protein they produce in the course of their life, "keratin." This protein is responsible for specific, important skin functions.

The melanocytes: Interposed between the keratinocytes of the basal layer there are "melanocytes" that synthesize "melanin," the pigment responsible for skin colour. The number of melanocytes can vary according to body area and are usually present as a ratio of the number of keratinocytes.

Biochemistry of melanin: Melanin is the pigment contained in the structures called melanosomes produced by the melanocytes. It is transferred to the surrounding epidermal keratinocytes, which maintain functional contact forming an epidermal melanin unit.

Langerhans cells: These cells are situated above the basal layer and, like the melanocytes, have a dendritic appearance. The Langerhans cells unite against exogenous antigens and "present" them to both skin and lymph node T lymphocytes. They are also involved in immune surveillance against viral and tumor antigens.

Merkel cells: These cells are found mainly in certain areas of the body: The fingertips, the oral mucosa, the lips, and the hair follicles. Merkel cells are considered as "tactile receptors," that is they are the structures responsible for our sense of touch.

The dermis: The dermis is positioned below the epidermis and is the tissue that supports the skin and its annexes (hair nails, etc.). Its thickness varies from area to area, being thinnest on the eyelids and thickest on the back. The dermis tends to become progressively thinner with age. This layer is formed by cells, fibres, and ground substance is richly innervated and vascularized. The most abundant cells are the *fibroblasts.* These cells are the production site of the other dermal components: Both the fibres of the dermis and the ground substance are synthesized within the fibroblasts. In addition to fibroblasts, *mastocytes* (mast cells), *lymphocytes,* and *histiocytes* are present.

The hypodermis: The hypodermis is situated below the dermis and is composed of "adipocytes" grouped into "lobes" separated by an area of connective tissue. The thickness of the hypodermis varies considerably according to the body site, nutritional state, and sex of the individual. Adipose cells are characterized by the remarkable quantity of lipids they contain. These lipids are grouped into a single globule in the cytoplasm, so large that the nucleus is forced to occupy a peripheral position. In fact, the distribution of subcutaneous fat is a strictly hormone-dependant secondary sexual characteristic. The number of adipose cells changes in the first phases of child development, at first increasing and then remaining stable. During puberty in women there is an increase in subcutaneous fat predominantly in the area of the buttocks, hips, thighs and breasts. In men, on the other hand, the increase in lipid content is in the area of the torso and abdomen.

Skin Cosmeceuticals

Protecting and preserving the skin is essential to good health. Cosmetics and skin care products are the part of everyday grooming. Our skin, the largest organ in the body, separates, and protects the internal environment from the external one. Environmental elements, air pollution, exposure to solar radiation as well as normal aging process cause cumulative damage to building blocks of skin—DNA, collagen, and cell membranes. Use of cosmetics or beauty products will not cause the skin to change or heal; these products are just meant to cover and beautify.

Cosmeceuticals being cosmetic products having medicinal or drug-like benefits are able to affect the biological functioning of skin owing to type of functional ingredients they

contain. There are skin-care products that go beyond coloring and adorning the skin. These products improve the functioning/texture of the skin by encouraging collagen growth by combating harmful effects of free radicals, thus maintaining keratin structure in good condition and making the skin healthier.

Sunscreen Agents

Sunscreen agents are used to prevent sunburns. The use of sunscreen agents and limiting the exposure to sun prevents early wrinkling and skin cancer (Fig. 6.4).

Chemical Sunscreen Agents

It contains organic (carbon-based) compounds, such as oxybenzone, octinoxate, octisalate and avobenzone, which creates a chemical reaction and works by changing UV rays into heat, then releasing that heat from the skin. It is often referred to as a chemical or organic absorber.

It protects the skin from the sun by absorbing the ultraviolet (UV) and visible sun rays, while physical sunscreen agents reflect, scatter, absorb, or block the rays. Ideally, coverage should include protection against both UVA and UVB sunrays. The sun protection factor (SPF) that is present on the label of these products reflects the minimum amount of UVB sunlight that is needed with that product to produce redness on sunscreen protected skin as compared with unprotected skin. Sunscreen products with high SPFs provide more protection against the sun.

Physical Sunscreen Agents

Physical sunscreen, unlike chemical sunscreen, contains active mineral ingredients, such as titanium dioxide or zinc oxide, which mainly works by sitting on top of the skin to deflect and scatter damaging UVA rays away from the skin. It is often referred to as a physical blocker.

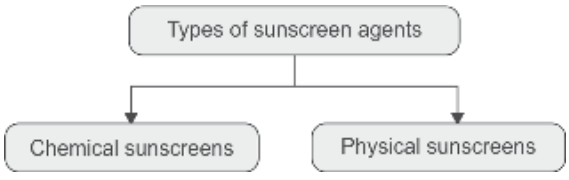


Fig. 6.4: Types of sunscreen agents

The following sunscreen agents have been recommended by the US Department of Health:

- Cycloform (isobutyl p-aminobenzoate)
- Propylene glycol p-aminobenzoate
- Monoglyceryl p-aminobenzoate
- Digalloyl trioleate
- Benzyl salicylate and benzyl cinnamate (2% each).

Moisturizing Agents

Stratum corneum is the primary barrier of the skin whose one of main purpose is to keep inside in and outside out. This barrier is richin cholesterol, free fatty acids, and ceramides. Many oily preparations have been used to maintain the fluidity of the skin (mineral oil, lanolin, cyclomethicone, etc.). Water from the stratum corneum gets evaporated very quickly leading to dehydration. This dehydration of skin can be averted by using moisturizers which provide flexibility to the skin.

Humectants are cardinal ingredients of the moisturizing formulations. Humectants also help in preventing drying out of the formulations. When moisturizers are applied to the skin, a thin film of humectants is formed which retains moisture and imparts better appearance to the skin. Moisturizers by hydrating the skin make the stratum corneum softer and can even alter physiology of skin. Ceramide containing moisturizers are very popular as these contain the same balance of lipids as our skin.

Examples:

1. Ceramides: Help to treat eczema, and can even be used for dry skin.
2 Fluocinolide reduces eczema.
3. Black cohosh, soy extract, and vitamins A and E augmenting the skin's natural moisture balance.

4. Complex mixture of hyaluronic acid and complex containing green tea leaf extract, and glutathione are also promising moisturizing agents.

Skin Lightening Agents

Hyperpigmentation is the changing of color intensity of the skin to darker hue, which is due to an increased amount of melanin in the epidermis, the dermis, or both. This change can be due to pathophysiologic processes: Melanocytosis (increased number of melanocytes) and melanosis (increased amount of melanin). Skin lightening agents work best when melanosis or melanocytosis is confined to the epidermis. Standard dermatologic agent for skin lightening is hydroquinone but its safety is questionable, leading to the use of alternative agents such as retinoid, mequinol, azelaic acid, arbutin, kojic acid, aleosin, licorice extract, ascorbic acid, soy proteins, and N-acetyl glucosamine.

The Hair System

The entire surface of the skin is supplied with hairs, but on the head the hairs are longer and more pigmented. There are three types of hair:

1. Vellus hair
2. Terminal hair
3. Lanugo hair

Anatomy and Histology of Hair (Fig. 6.5)

Hairs develop from the hair follicles, which are true organs formed by the invagination of the epidermis during the fetal development. These organs are divided into three main parts:

1. The infundibulum is the portion from the opening on the skin surface to the mouth of the sebaceous gland duct.
2. The isthmus is the section between the sebaceous gland duct and the point of intersection with the hair erector muscle.
3. The inferior portion extends from the erector muscle to the bulb of the hair follicle.

The *hair root* is a generic term that includes the entire inferior portion and the isthmus. The *bulb* is the enlarged terminal part of the hair follicle in the root. The root produces the hair *shaft*, which is defined as the hair structure visible above the skin surface. Below the bulb the dermis re-enters the hair follicle, producing the *dermal papillae,* as the hair follicle is formed by introflexions of the epidermis; this re-establishes the junction with the dermis. In this way the hair follicle is surrounded by the basal membrane. In this region it is particularly thick and assumes the name *vitreous membrane,* because together with the basal membrane it forms a kind of connective sheath that surrounds the whole follicle. The part on the hair follicle between

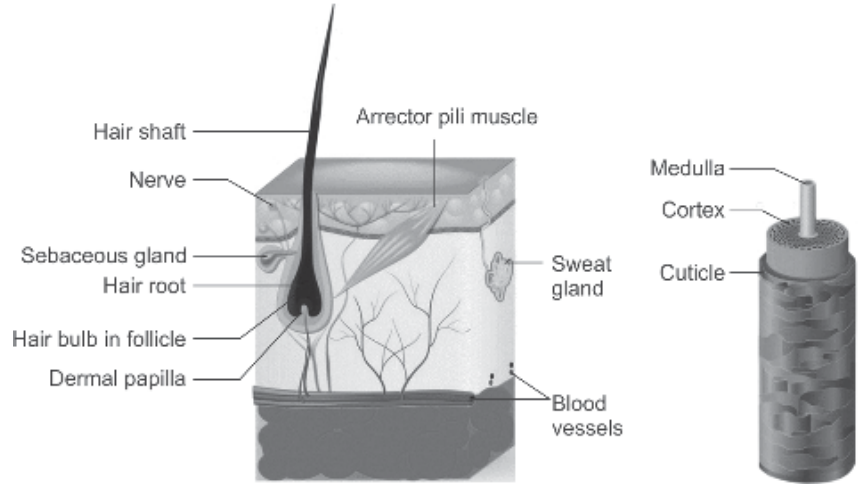


Fig. 6.5: Anatomy of hair

the bulb and the isthmus is known as the *keratogenous zone.* The maturation of the cells that produce the hair shaft occurs in this area.

The most important part of the hair follicle is the bulb. In the basal layer, immediately above the papillae, cells continuously divide and begin their ascent. Slowly as this process proceeds the cells subdivide in the layers that make up the follicle. In fact, if a hair is cut perpendicularly to the follicle one can easily see how, independently of the zones and structure described earlier, each of these is formed by the union of layers and from inwards towards the outside of the follicle we can recognize the following layers: The *medulla, cortex,* and *cuticle.* These three layers form the hair shaft. The cuticle is followed by the *cuticle of the internal epithelial sheath, Huxley's layer,* and *Henle's layer.* Beyond these layers the *external epithelial sheath* begins and this, too, is composed of cell layers becoming increasingly thinner from the epidermal surface to the bulb. In the germinative layer, or *hair matrix,* the keratinocytes are in contact with melanocytes, which are present only in this region. Here the melanocytes produce the pigment that will give rise to our hair coloring. The connective sheath also envelops the sebaceous gland and the hair erector muscle. The latter structure, important in furry animals in controlling the angle of the hair and so regulating heat exchange, is all but useless in man, nevertheless, this thin muscle is able to raise the hair. The follicles are set obliquely to the skin's surface and the erector muscle, by contracting and nipping both the follicle and the epidermis, are able to raise the hair. This is the phenomenon of *horripilation,* commonly called goose flesh, which occurs during shivering due to cold or fear.

Hair Cosmeceuticals

The appearance of the hair is a feature of the body over which humans, unlike all other land mammals, has direct control. Hair care, color, and style play an important role in people's physical appearance and self-perception. But today's delineation of cosmetics from pharmaceuticals has become more complex through the development of cosmetics with physiologically active ingredients, i.e. cosmeceuticals. Shampooing is by far the most frequent form of cosmetic hair treatment. While shampoos have primarily been products aimed at cleaning the hair and scalp, current formulations are adapted to the variations associated with hair quality, hair care habit, and specific problems such as treatment of oily hairs, dandruff and for androgenic alopecia related to the superficial condition of the scalp. Cosmetics for the treatment of hair are applied topically to the scalp and hair. While they can never be used for therapeutic purposes, they must be harmless to the skin and scalp, to the hair, and to the mucous membranes and should not have any toxic effect, general or local, in normal conditions of their use.

A hair cosmeceutical product includes—conditioning agents, special care ingredients, and hair growth stimulants. Conditioning agents are intended to impart softness and gloss, to reduce flyaway and to enhance disentangling facility. A number of ingredients may be used, mostly fatty ingredients, hydrolyzed proteins, quaternized cationic derivatives, cationic polymers, and silicons. Special care ingredients are aimed at modifying specific problems relating to the superficial scalp. These shampoos are formulated around one or more specific ingredients selected for their clinical effectiveness in these conditions. Accordingly, current antidandruff ingredients are virtually all-effective antifungal agents—zinc pyrithione, octopirox, and ketoconazole. Hair growth stimulants cannot be expected to have any impact on hair growth due to short contact time and water dilution. There are numerous cosmeceutical eye creams that nourish the skin with natural emollients and beneficial nutrients. The other functional ingredients include butcher's broom, chamomile, and vitamin E, antioxidants—vitamins A, C and E, green tea and tiare flower, *Ginkgo*

biloba and also cucumber, calendula and α-*bisabolol*, an active constituent of chamomile, to calm irritated skin. A key ingredient in the eye lifting moisture cream that treats puffiness, irritation, and also protects against future skin damage is yeast which helps to plump up the wrinkles.

CHARACTERIZATION OF COSMETICS

Physical Characterization

Appearance

Assessment and description of appearance are one of the easiest, most practical, and nevertheless powerful tests. It may be performed macroscopically, describing color, clearness, transparency, turbidity, and state of matter. In addition, microscopic investigation is recommended; taking microphotographs is useful for documentation.

Rheology

Rheological properties (viscosity, consistency) are important characteristics of most types of cosmetic care products because they have an impact on preparation, packaging, storage, application, and delivery of actives. Thus these properties should be assessed for characterization and quality control of the product. Most disperse systems and thus cosmetic care products show non-Newtonian flow behavior, namely pseudoplastic, plastic, or dilatant behavior. A wide variety of techniques and methods have been developed to measure viscosity properties. These procedures can be classified as either absolute or relative. The absolute either directly or indirectly measures specific components of shear stress and shear rate to define an appropriate rheological function. Methods used for absolute viscosity measurements are flow through a tube, rotational methods, or surface viscosity methods. Methods used for relative viscosity measurements are those using orifice viscometers, falling balls, or plungers. Such instruments, although they do not measure stress or shear rate, offer valuable quality-control tests for relative comparison between different materials. Apparatus based on rotational or even oscillating principles to assess viscoelastic properties are state-of-the-art.

pH

Measurement of pH value (concentration of hydrogen ions) in aqueous vehicles (solutions, suspensions, o/w emulsions, gels) is a valuable control mean. First of all, if possible, a pH value in the physiological range is generally targeted, ideally similar to that of the skin or the specific application site, to prevent irritation. Many reactions and processes depend on pH, e.g. efficacy of antimicrobial preservatives, stability and degradation of substances, and solubility. Thus, pH measurement is a ''must,'' and it is easily performed with the available measurement systems.

Homogeneity

In many cases, at a first step, homogeneity may be assessed visibly; precipitation in a solution or distinct phase separation in an emulsion is easily detected. Nontransparent, multiphasic systems are more difficult to check. In these cases, microscopic investigation of representative samples is suggested along with quantitative assays regarding active ingredients (uniformity of content).

Droplet or Particle Size and Distribution

The physical stability of colloidal systems as well as emulsions or suspensions partially depends on the particle size. In particular, preparations containing small particles with identical electrical charge are more resistant to flocculation and sedimentation than systems containing larger or uncharged entities. Similarly, reduced particle size is an indicator of improved kinetic stability of emulsions or suspensions. For that reason, determination of particle size and size distribution is an important characterization method. Various optical methods are available:

1. Perhaps the most commonly used method today is based on laser diffraction, suitable to measure solid particles and also dispersed droplets under special conditions, size range 1 to 600 (mm).
2. Dynamic light scattering, also known as photon correlation spectroscopy, is used for measuring micelles, liposomes, and submicron suspensions (size range 0.003–3 mm).
3. Optical or electron microscopy is a further method of choice.

Chemical Characterization

Besides physical characterization, chemically based investigations are indispensable to assess the quality of a product. It is well known that the quality and composition of a vehicle can influence the chemical stability of ingredients. Many reactions, such as ester hydrolysis or other degradations, may be enhanced or sustained by a change in pH, presence of catalytic or stabilizing agents, respectively. Thus, development and optimal selection of the best vehicle are supported by chemical stability investigations.

Biological Characterization

Further important assessment methods are based on biological tests. This is to evaluate and validate the desired targeted effects *in vivo* after application of the product. Examples include hydration of the skin, protection against sun radiation, and protection against skin irritating substances during work. This subject is treated in other chapters of this textbook.

Sensory Assessment

The sensory assessment is a useful tool for product and concept development and for quality control in the cosmetic industry. Although a very subjective and liable method, valuable data are obtained if sensory assessment is conducted in a systematic way. The consistency of a material can be assessed by using three attributes: Smoothness, thinness, and warmth.

Internally, the skin shelters and protects all the physiochemical phenomenon necessary for life, externally it is a barrier against mechanical forces, both physical and chemical, which can be hostile to life.

HERBS USED FOR SKIN

Coconut oil (or butter) is extracted from mature coconuts that have fallen to the ground. It is stable at high temperatures (up to 76.6°C). It is a colorless to pale brownish yellow oil with a melting point ranging from 23 to 26°C. Modified coconut oil containing polyunsaturated fatty acids in the form of mono-, di- and triglycerides, is useful as a constituent of a barrier lipid mixture in cosmetic and pharmaceutical formulations to protect and prevent drying of the skin. In Ayurvedic medicine, coconut oil is said to nourish the body and increases strength while application of coconut oil to the skin is said to help fixation of vitamin D in the body. The cosmetic application of coconut oil in hair and skin oil includes prevention of dandruff and providing emolliency, in shampoos it aids value, it is also used to prepare massage oils and beauty care products.

Sunflower oil: Sunflower seeds from *Helianthus annuus* (compositae), contain polyunsaturated fats, rich in triglycerides of linoleic acid, an essential fatty acid needed by the body to maintain good skin condition. Sunflower oil is rich in essential fatty acids, which have important regulatory actions on skin elasticity and moisture

1. It is highly recommendable to formulate cosmetic products.
2. To protect the integrity of skin (anti-aging products) and hair (color protection products).
3. To formulate cosmetic products with photoprotective activity.
4. To formulate cosmetic products to treat hair loss, to formulate cosmetic products with hair conditioning activity.

5. To formulate cosmetic products with purifying and antiseptic activity.

Studies indicate that cutaneous application of the sunflower oil increases the linoleic acid levels of the skin, lowers transepidermal water loss, and helps to eliminate scaly lesions common in patients with essential fatty acid deficiency.

Olive oil: *Olea europaea* (oleaceae) fruit and oil; used to moisturize dry skin, and as a lip balm, shampoo, hand lotion, soap, massage oil and in dandruff treatment. Olive oil contains fatty acids, triglycerides, tocopherols, squalene, carotenoids, sterols, polyphenols, chlorophylls, volatile and flavour compounds. The extracts of mixtures of olive fruits, leaves and stems show anti-inflammatory and active oxygen scavenging effects. The anti-inflammatory effect is exerted by both unsaponifiable and polar compounds, while the free radical-scavenging effect of virgin olive oil is due to the presence of polyphenols. It is applied topically to treat skin damage, such as contact dermatitis (particularly diaper area dermatitis), atopic dermatitis, xerosis, eczema (including severe hand and foot eczema), rosacea, seborrhoea, psoriasis, thermal and radiation burns, other types of skin inflammation and aging.

Turmeric: Turmeric is the rhizome of *Curcuma longa* L. (zingiberaceae). It is usually boiled, cleaned and dried, yielding a yellow powder. The major component is curcumin, which is responsible for most of the biological activities. Turmeric helps to remove hairs and impart color and improve complexion of skin. Several Sanskrit synonyms of turmeric indicate its color-improving property (such as: Varnadatri—one who gives color, indicates its use as enhancer of body complexion. It is also used for prevention, treatment or control of psoriasis and other skin conditions such as acne, wounds, burns, eczema, sun damage to the skin and premature aging, due to inhibiting the activity of phosphorylase kinase. Turmeric oil is used as aromatherapy and in perfume industry apart from religious, cultural uses.

Pumpkin: Fatty acids isolated from *Cucurbita pepo* (cucurbitaceae) seed oil. It contains main fatty acid components being palmitic (10.68%), palmitoleic (0.58%), stearic (8.67%) oleic (38.42%) linoleic (39.84%), linolenic (0.68%), gadoleic (1.14%), total saturated fatty acids (19.35%), and total unsaturated fatty acids (80.65%). The people of Central America and India rub the oil extracted from the seeds of pumpkin on herpes lesions, venereal sores, acne vulgaris and stubborn leg ulcers which refuse to heal up.

Pumpkin is a storehouse of vitamins, mineral and other healthy nutrients. Whether it is the pulp or the seed, pumpkin is magnificent for your health and can offer some inconceivable benefits. Pumpkin leaves are also applied as a poultice on sprains and pulled ligaments. The roots are made into an infusion and used on syphilitic sores, herpes lesions, pimples and blackheads.

Onion: The common red onion, *Allium cepa* (liliaceae), has been used traditionally for its beneficial effects when used externally as a poultice for acne, boils, abscesses and blackheads to draw out the infection, decrease inflammation and speed healing.

Ginseng: Ginseng is an important traditional drug used for more than 2000 years. *Panax ginseng* is a representative medicinal herb belonging to the Araliaceae family, which is seven major species of ginseng distributed throughout East Asia, Central Asia, and North America. Ginseng is reported to activate the skin's metabolism, reduce keratinization, provide moisture and soften, alleviate wrinkling and enhance skin whiteness. The major active components of ginseng, ginsenosides, are known to exhibit antiaging, antioxidant, and anti-inflammatory activities. It also possesses skin protective and improving effects, as well as protection against excessive sun exposure using *in vitro* and *in vivo* models.

Tea: *Camellia sinensis* (theaceae) yields both black (red) and green tea. It contains more than 500 chemical compounds, including polysaccharides, tannins, flavonoids, amino acids, vitamins and caffeine. The fermentation process of tea leaves results in black tea while to produce green tea, the leaves are steamed immediately after harvest and then dried.

Green tea: A *Cammelia sinensis* leaf contains flavanols, commonly known as catechins, consists of four major polyphenolic catechins. (-) Epigallocatechin-3-Ogallate (EGCG) is the most abundant and biologically active component, having antioxidant effects. In addition, it is used for prophylaxis, treatment and/or care of dry skin conditions, by stimulating the formation of ceramides and sphingolipids in the skin and thus reinforcing the lipid barrier.

The polyphenols have the potential to protect skin when combined with traditional sunscreens as they found to be particularly potent at suppressing the carcinogenic activity of UV radiation and exerting broad protection against other UV-mediated responses such as sunburn, immunosuppression, and photoaging.

Black tea: Black tea extracts contain polyphenols in a lower amount, and show a rather weaker protective effect against free radicals than green tea, but are still considered to be a good antioxidant.

Grape seed: The seeds of *Vitis vinifera* L. (Vitaceae) and its many varieties contain polyphenolic proanthocyanidins, which in turn can bind to each other to form oligomers known as procyanidins. Grapes contain fruit acids, and the unripe fruit contains oxalic acid. Its seeds contain 6–20% oil, phenols, carbohydrates and fruit acids. The procyanidins are strong antioxidants (compared with vitamins C and E), by inhibition of lipid peroxidation. Grape seed extracts are useful in antiaging and skin-lightening cosmetics as it shows tyrosinase-inhibiting activity.

Chamomile: German chamomile (*Matricaria recutita* L.; often referred to as true chamomile), or the *Roman chamomile* (*Anthemis nobilis* Linn.) are both members of the family compositae. The both plants share a similar spectrum of chemical components, though not in the same ratios. Extracts of the plant are used in the form of ointments, lotions and inhalations intended for local application. Chamomile extract, essential oil and isolated constituents possess anti-inflammatory effects and are useful for treating inflammation of skin and mucous membranes, eczema and as an antipruritic adjunct in the treatment and prevention of skin disorders.

Fenugreek: Fenugreek (*Trigonella foenum-graecum L.*) locally known as "methi" belonging to the family leguminosae and subfamily papilionaceae is widely used as spice and condiment to add flavour in various foods. It was also named, trigonella, from latin language that means "little triangle" due to its yellowish-white triangular flowers. The fenugreek extracts are used in cosmetic soaps.

Jojoba: Jojoba oil (*Buxus chinensis or Simmondsia chinensis* (link). *C. schneider,* family Buxaceae), contains fatty acids of broad spectrum such as arachidonic, linolenic, linoleic and oleic as well as triglycerides which have good compatibility with the natural sebum in the skin.

The peanut-sized seed is cold-pressed and expressed to yield about 50% of liquid wax known as jojoba oil. It is a rich extract used in cosmetic preparations, not only as humectant, but it also creates a protective film over the skin that keeps in moisture. Jojoba oils and its hydrogenated derivatives are non-greasy lubricant, therefore, may be useful in the formulation of creams, lotions, soaps, lipsticks and other preparations designed to be spread onto the skin or hair.

Licorice root: *Glycyrrhiza glabra* Linn is one of the most extensively used medicinal herb from the ancient medical history of Ayurveda. It is

also used as a flavouring herb. The word Glycyrrhiza is derived from the Greek term *glykos* (meaning sweet) and *rhiza* (meaning root). *Glycyrrhiza glabra* Linn, commonly known as 'liquorice' and 'sweet wood' belongs to Leguminosae family. As literature suggests that liquorice extract can be used efficiently to formulate cosmetic products for the protection of skin and hair against oxidative damage. It is responsible for its powerful antioxidant activity by means of significant free radical scavenging, hydrogen-donating, metal ion chelating, anti-lipid peroxidative and reducing abilities. The extract of liquorice is reported to be an effective pigment lightening agent. It is the safest pigment-lightening agent known with least side effects. Due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity. Licorice is also used for skin irritations and in cosmetics for acne and sunburn.

Aloe vera: Aloe (*Aloe barbadensis*) is an important and traditional medicinal plant belonging to the family Liliaceae. Aloe's benefits can be attributed due to proteins, carbohydrates (including mucopolysaccharides), vitamins (including B_1, B_2, B_3, B_6, C, and folic acid) and minerals. These nutrients are beneficial individually as well as synergistically soothe, heal, moisturize and regenerate the skin. Many cosmetic companies add sap or other derivatives from aloe to products such as makeup, tissues, moisturizers, soaps, sunscreens, incense, razors and shampoos.

Its cosmetic applications are to stimulate the production of collagen and elastin that prevents aging of the skin, used in soaps, shampoos, creams and lotions for beauty purposes, in addition, it lightens the dark spots on the face and reduces the intensity of pigmentation, while applying topically, the gel acts as best moisturizer, removes dead skin cells and rejuvenates the skin and also it hastens the skin repair and hydrates your skin resulting in healthy and glowing skin. Aloe gel can be applied topically as an emollient for burns, sunburn and mild abrasion, and aloe has antibacterial, antifungal, antiviral, antioxidant, antihistamine and anti-inflammatory effects. Aloe gel is also described as a cleanser, anaesthetic, antiseptic, antipyretic, antipruritic, nutrient, and moisturizer.

Cucumber or *Cucumis sativa* Linn. (Cucurbitaceae), is cooling, healing and soothing to irritated skin, whether caused by sun, or the effects of a cutaneous eruption. Analysis of the fruit shows that it is low in nutrient value and little vitamin A but it is a good source of iron, calcium, and vitamins B and C. It is used for the treatment of hyperpigmentation in cosmetic preparations. The cucumber extract and lemon extract both are used; surprisingly, two ingredients do not interfere with each other, and instead increases lightening capabilities.

Antiaging

***Rhodiola rosea*:** It is commonly known as golden root, roseroot, king's crown, lignum rhodium. It is a plant in the Crassulaceae family that habitats in cold regions of the world. It grows mainly in dry sandy ground at high altitudes in the arctic areas of Europe and Asia, *R. rosea* is rich in phenolic compounds, known to have strong antioxidant properties.

Carrot: It is obtained from the plant *Daucus carota* belonging to family Apiaceae. The richness of a valuable herb is due to vitamin A along with other essential vitamins. Carrot seed oil is used as anti-aging, revitalizing and rejuvenating agent. The carrot gets its characteristic and bright orange colour from β-carotene, and lesser amounts of α-carotene and γ-carotene. α and β-carotenes are partly metabolized into vitamin A in humans.

Gingko: *Ginkgo biloba* L. family Ginkgoaceae is the most commercialized medicinal plant worldwide**,** leaves and nuts have been used for thousands of years to treat various medical conditions, including poor blood circulation;

hypertension; poor memory, and depression. In addition, it is gaining a similar reputation as an antioxidant and anti-inflammatory agent. *Ginkgo biloba* belongs to, which grows to a huge size. *G. biloba* is chemically characterized in nutritional and bioactive components, namely due to fatty acids, sugars, organic acids, tocopherols, phenolics and flavonoids. Palmitic, α-linolenic and oleic acids were the main fatty acids found; fructose was the most abundant sugar; quinic acid is the most abundant organic acid and α-tocopherol is widely used in various cosmetic preparations and formulations.

Neem: Neem or margosa is a botanical relative of mahogany. It belongs to the family Meliaceae. *Azadirachta indica* is derived from the Persian. Azad = Free, dirakht = Tree, i-Hind = of Indian origin. It contains nimbin, nimbidin and nimbinene. A large number of medicinals, cosmetics, toiletries and pharmaceuticals are now based on neem derivatives because of its unique properties. Neem bark is cool, bitter, astringent, acrid and refrigerant. It is useful in tiredness, cough, fever, loss of appetite, worm infestation. It heals the wounds and is also used in vomiting, skin diseases and excessive thirst.

Antioxidants

Tamarind: Tamarind or *Tamarindus indica* L. of the Fabaceae, subfamily Caesalpinioideae consists of amino acids, fatty acids and minerals. The sweet acidic taste of tamarind is most distinguished characteristic of tamarind due to tartaric acid. Apart from it is rich source of sugars, excellent source of vitamin B and contains minerals. It exhibits high antioxidant capacity that appear to be associated with a high phenolic content. Biological activity assessment of tamarind seed was reported on the radical scavenging, lipid peroxidation reducing and anti-microbial activities including anti-inflammatory potential. In addition, it is also used in skin lightening and control of sebum in cosmetic formulations.

Vitamin C: It is necessary for the hydroxylation of proline, procollagen, and lysine. Vitamin C improves the changes caused by photo damage. Vitamin C has been used effectively to stimulate collagen repair, thus removing some of the effects of photo-aging on skin.

Vitamin E (Alpha-tocopherol): It is the major lipophilic antioxidant in plasma membranes and tissues. The term vitamin E collectively refers to 30 naturally occurring molecules (4 tocopherols and 4 tocotrienols), all of which exhibit vitamin E activity. Its major role is generally considered to be the arrest of chain propagation and lipid peroxidation by scavenging lipid peroxyl radicals, hence protecting the cell membrane from destruction.

HERBS USED FOR HAIR CARE

Depending on its moisture content, human hair consists of approximately 65–95% keratin proteins, and the remaining constituents are water, lipids (structural and free), pigment, and trace elements. Proteins are made up of long chains of various mixtures of some 20 or 50 amino acids. Each chain takes up a helical or coiled form. Among numerous amino acids in human hair, cystine is one of the most important amino acids. Every cystine unit contains two cysteine amino acids in different chains which lie near to each other and are linked together by two sulfur atoms, forming a very strong bond known as a disulfide linkage. In addition to disulfide bonds, hair is also rich in peptide bonds, and the abundant CO- and NH-groups present give rise to hydrogen bonds between groups of neighboring chain molecules. The distinct cystine content of various cellular structures of human hair results in a significant effect on their physical properties. High cystine content corresponds to rich disulfide cross-links, leading to high mechanical properties. The species responsible for colour in hair is the pigment melanin, which is located in the cortex of the hair in granular form. An average

head contains over 100,000 hair follicles, which are the cavities in the skin surface from which hair fibers grow. Each follicle grows about 20 new hairs.

Plant materials can be used as hair growth stimulants, hair colorants and dyes, and in a number of hair and scalp complaints such as dandruff.

A. barbadensis gel is used traditionally for hair loss, and for improvement in hair growth following alopecia. Aloenin is the major constituent responsible for promoting hair growth without irritating the skin. Aloe vera has been cited as a treatment for brittle hair, but with no evidence to substantiate this claim.

Henna or *Lawsonia alba L.* (Lythraceae) has been cited as a growth accelerator and was used in an ancient Egyptian formula to cure the loss of hair. The incidence of contact dermatitis appears to be extremely rare with the use of henna, since henna leaf extracts have mild anti-inflammatory and antiallergic action and analgesic effects.

Salvia officinalis L. (Labiatae) also called 'common sage', 'true sage' or 'garden sage' is used as a lotion to improve the condition of hair and skin. Claims of its use, alone or with rosemary, to maintain the sheen of dark curly hair, and to strengthen and stimulate hair growth have been made. The major *S. officinalis* constituents responsible for the effect on hair are the tannins, saponins, as well as borneol and camphor.

Rosemary or *Rosmarinus officinalis* Linn. (Labiatae) is an aromatic herb surrounded by tradition and legends but with important culinary, medicinal and cosmetic properties. In folk medicine it is used to stimulate growth of hair as a rinse. The most important constituents of rosemary are thought to be caffeic acid and its derivatives such as rosmarinic acid; these compounds have antioxidant effects.

Dandruff Treatment

Dandruff is a major problem, yet little is known about the underlying mechanism and subsequent biochemical changes that occur in the scalp skin and lead to its manifestation. Dandruff is also associated with a dramatic decrease in free lipid levels, with significant decreases in ceramides, fatty acids and cholesterol. Thus the epidermal water barrier is impaired in the scalp of dandruff sufferers, and the perturbed barrier leaves sufferers more prone to the adverse effects of microbial and fungal toxins, and environmental pollutants, thus perpetuating the impaired barrier.

Traditionally sage (*Salvia officinalis* L.) is an old favourite for dandruff, loss of hair and greasy hair and skin. An extract of sage massaged into the scalp can control dandruff, falling hair or loss of hair if the papilla is dormant and not destroyed.

Rosemary is claimed to be a conditioner for greasy hair, a rinse and a tonic that gives body and sheen to hair, and infused fresh or dried rosemary and sage can be used as a daily rinse for dandruff treatment.

Thyme or *Thymus vulgaris* L. (Labiatae) is also claimed to inhibit dandruff, and used in a scalp rub, it prevents hair falling out, and rinses containing rosemary and thyme promote natural hair health.

Garlic or *Allium sativum* (L. Liliaceae) lotion can help to control dandruff. It has been used since ancient times as a vegetable with many properties, including antiseptic, tonic, antioxidant, anti-inflammatory, antibacterial and antifungal effects. Garlic should not be placed directly on the skin since it may cause blisters and a burning sensation in some people or contact dermatitis and allergic reactions in others.

English Walnut or *Juglans regia* L. (Juglandaceae), leaves are used in traditional medicine for external applications such as eczema, acne, loss of hair, scalp itching, peeling and dandruff; and as an adjunctive emollient itch-relieving treatment in skin disorders; as a trophic protective agent for cracks, abrasions, frostbite, chaps and insect bites to treat sun burns and for nappy rashes.

Juglans nigra refers to the black walnut, whose bark is used for dandruff and other

scalp problems. Hair coloring vegetable dyes can usually be recommended to patients sensitized to oxidative dyes, due to their low allergenic power. The use of natural dyes on the hair has not made great progress and this is due firstly, to the fact that natural dyes are not very stable in solution, and are prone to oxidation, discoloration, pH color shift and fading. Secondly, a single natural dye may not give the right colour, and only henna or walnut seem to be suitable to color the hair. However, many shades can be obtained by mixing with the leaves of other plants.

The leaves of *Lawsonia inermis*, known as henna, has been applied since ancient times for decorating and dyeing hands and feet, to impart shades of dark red, and for the treatment of certain skin disorders. The compound lawsone, a brown powder isolated from the leaves, is responsible for the red color in henna. It is used as a staining agent, due to the strong binding of lawsone to the hair, probably upon reaction of thiol groups with keratin. If the hair is dyed with henna and then treated with a hot decoction of *Allium cepa* (onion) skin, a coppery color will be obtained. The incidence of contact dermatitis from using henna appears to be rare but possible.

Curcumin is the pigment of the spice turmeric and will also give a range of colour from yellow to a deep orange. Turmeric contains three major curcuminoids, of which curcumin is the most significant, and these are responsible for the yellow color of the herb.

Sweet orange (*Citrus sinensis* [L.] Pers.) oil is composed largely of terpene hydrocarbons which is a source of flavour and fragrance compounds, it has more than 90% limonene and although it is primarily used in flavours, it does find a use in soap fragrances.

Grapefruit (*Citrus paradisica* Macfad.) oil is chemically similar to orange oil but it has a distinctive smell which is largely attributed to a ketone called nootkaton. Grapefruit oil does not find very wide use in perfumery.

Chamomile oil: The ability of chamomile to reduce inflammation is one of its most highly prized features due to the presence of flavonoids. It is safe for skin care, and it is also credited with a gentle analgesic effect. Its effects as anti-inflammatory, antierythema and antipruritic, at the same time as being gentle, soothing and antiseptic, may help in whitening age spots, take the soreness out of a boil, minor wound, burn, or an insect bite, or used for dry skin, windburn, sunburn, or even chronic skin conditions such as acne and psoriasis.

Geranium oil: *Pelargonium graveolens* (L.) (Geraniaceae), obtained through steam or water plus steam distillation of shoot biomass, is extensively used in the fragrance industry and in aromatherapy. Geranium oil is a cleansing, toning and sharpening oil and is so helpful with those problems that come with greasy, over-oily skin, acne, congested skin and eczema. Care should be taken since there is the possibility of contact dermatitis in hypersensitive individuals. It is a very important component of high grade perfumes due to its strong rose-like odor.

Lavender oil: Essential oils distilled from members of the genus Lavandula have been used both cosmetically and therapeutically for centuries. It is extensively employed in all types of soaps, lotions and perfumes, with the most commonly used species being *Lavendula angustifolia, L. latifolia, L. stoechas* and *L. intermedia*. Among the claims made for lavender oil are that it is antibacterial, antifungal and effective for burns and insect bites. This oil in the herbal tradition is said to encourage cell growth and so should be used to help with mending and regeneration in all kinds of skin ailments: Bites, stings, boils, burns, stretch marks, rashes, spots, cold sores, sunburns. Lavender oil inhibits immediate-type allergic reaction in mice and rats. Topical and intradermal lavender oil inhibited the ear swelling response in mice and passive cutaneous anaphylaxis in rats.

Amla: Amla is the name given to the fruit of a small leafy tree (*Emblica officinalis*), which grows throughout India. There are mainly four species of roses for oil production. These are *Rosa damascena* Mill., *R. gallica* L., *R. moschata* Herrm. and *R. centifolia* L. Rose oil and rose water have many therapeutic effects. Rose oil helps soothe the mind and heals depression, grief, nervous stress and tension. It also helps to heal wound and skin health.

Eucalyptus oil: There are around 700 different species of Eucalyptus in the world, of which at least 500 produce a type of essential oil. It is produced by steam distillation from the leaves of Eucalyptus species (*E. cinerea* F. Muell., *E. baueriana* F. Muell., *E. smithii* R. T. Baker, *E. bridgesiana* R. T. Baker, *E. microtheca* F. Muell., *E. foecunda* Schau., *E. pulverulenta* Sims, *E. propinqua* Deane and Maiden, *E. erythrocorys* F. Muell.), etc. They are widely used in the preparation of liniments, inhalants, cough syrups, ointments, toothpaste and also as pharmaceutical flavours. The European Pharmacopoeia monograph for Eucalyptus oil sports a chromatographic profile: 1, 8-cineole (eucalyptol; not less than 70%), limonene (4–12%), α-pinene (2–8%), α-phellandrene (less than 1.5%), β-pinene (less than 0.5%), camphor (less than 0.1%).

Ayurveda has numerous natural medications wherein the most common herbs include neem, kapoor (naphthalene), and henna, hirda, behada, and amalaki, magic nut, bringaraj, rosary pea, sweet flag, cashmere tree and mandor.

Henna: Henna comes from the plant *Lawsonia inermis* family Lythraceae, which contain a dye molecule called lawsone, which when processed produces henna powder. Besides lawsone other constituents present are gallic acid, glucose, mannitol, fats, resin (2%), mucilage and traces of an alkaloid. Leaves yield hennatannic acid and an olive oil green resin, soluble in ether and alcohol. It is highly praised both for its high vitamin C content and for the precious oil, which is extracted from its seeds and pulp and used as a treatment for hair and scalp problems. It is used in eye syndromes, hair loss, and children ailments, etc.

Shikakai: *Acacia concinna* Linn. (Leguminosae) is a medicinal plant that grows in tropical rainforests of southern Asia. The fruits of this plant are used for washing hair, for improving hair growth, as an expectorant, emetic, and purgative. The powder of *Acacia concinna* linn shows the presence of saponins, alkaloid, sugar, tannin, flavanoids, anthraquinone glycosides.

Regulatory Aspects

The claims made about drugs are subject to high scrutiny by the Food and Drug Administration (FDA) review and approval process, but cosmetics are not subject to mandatory FDA review. Much confusion exists regarding the status of 'cosmeceuticals.' Although there is no legal class called cosmeceuticals, this term has found application and recognition to designate the products at the borderline between cosmetics and pharmaceuticals. Cosmeceuticals are not subject to FDA review and the Federal Food, Drug and Cosmetic Act do not recognize the term itself. It is also often difficult for consumers to determine whether 'claims' about the actions or efficacies of cosmeceuticals are in fact valid unless the product has been approved by the FDA or equivalent agency. Some countries have the classes of products that fall between the two categories of cosmetics and drugs: For example, Japan has 'Quasi-drugs'; Thailand has 'controlled cosmetics' and Hong Kong has 'cosmetic-type drugs'. The regulations of cosmeceuticals have not been harmonized between the USA, European, Asian and other countries.

India's Cosmetic Market Scenario

The cosmetic industry in India is classified into skin care, hair care, oral care, fragrances and color cosmetic sections and many more. The

current market for cosmetic in India is USD 6.5 billion and is expected to reach ~ USD 20 billion with CAGR rate of 25% by 2025. On the other hand, the global cosmetic market is expected to reach ~ USD 450 billion with CAGR rate of 4.3% by 2025. This shows that by 2025 India will contribute to 5% of the total global cosmetic market and will become one of the top 5 leading global markets in terms of revenue. Many international brands such as Mac Cosmetics, Avon, Estée Lauder, L'Oréal, and Willa professionals established in India because of increased demand of products, improving purchase power and increasing image consciousness of Indian clientele. The awareness about cosmetics and developing fashion consciousness are created by social media and favorable demographics and thus plays an important role. The awareness in the public of possible dangers in regularly using chemical formulations caused switching to 'safer' herbal and ayurvedic products such as Himalaya, Biotique, Dabur, Lotus, Patanjali, etc. The increasing demand for cosmetics led to the introduction of products from luxury brands like Shahnaz Hussain, Forest Essentials and Kama Ayurveda. The market of herbal product is not only restricted to India but also expanding in overseas market.

COSMECEUTICAL PREPARATIONS IN TRADITIONAL TEXTS OF AYURVEDA

MARKETED PREPARATIONS OF COSMECEUTICALS BY PHARMACEUTICAL COMPANIES

CONCLUSION

Herbal cosmetics are prepared, using permissible cosmetic ingredients to form the base in which one or more herbal ingredients are used to treat different skin ailments and for the beautification. The chemical formulation of all these cosmetic products includes addition of various natural additives like waxes, oils natural color, natural fragrances and parts of plants like leaves, etc.

The demand of herbal cosmetic is rapidly expanding. The advantages of herbal cosmetics are lower cost, side effects free, environmental friendly, safe to use, etc. Also has a great future ahead as compared to the synthetic cosmetics. Proper regulation of these herbs and standardization will lead to tremendous and significant growth in herbal cosmetics field

Unit V

Evaluation, Status, Bioavailability and Pharmacovigilance of Herbal Formulation

CHAPTER 7

Evaluation of Quality, Efficacy and Safety of Herbal Formulation

Quality: A major concern—quality of herbs has become a major concern and has to be assured at all stages—herbal raw materials, processing of herbals and finished herbal medicines.

Three pillars of herbal drugs and their rational use with quality control of herbal drugs are shown in Figs 7.1 and 7.2.

The standardization of crude drug materials includes the following steps:

1. Authentication (stage of collection, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and histological analysis, taxonomical identity, etc.)
2. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)
3. Organoleptic evaluation (sensory characters—taste, appearance, odor, feel of the drug, etc.)
4. Tissues of diagnostic importance present in the drug powder.
5. Ash values and extractive values.
6. Volatile matter
7. Moisture content determination
8. Chromatographic and spectroscopic evaluation. TLC, HPTLC, HPLC methods will provide qualitative and semi-quantitative information about the main active constituents present in the crude drug as chemical markers in the TLC fingerprint evaluation of herbals (FEH). The quality of the drug can also be assessed on the basis of the chromatographic fingerprint.
9. Determination of heavy metals, e.g. cadmium, lead, arsenic, etc.

   WHO guidelines for standardization of herbal formulations are shown in Fig. 7.3.
10. Pesticide residue: WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene,

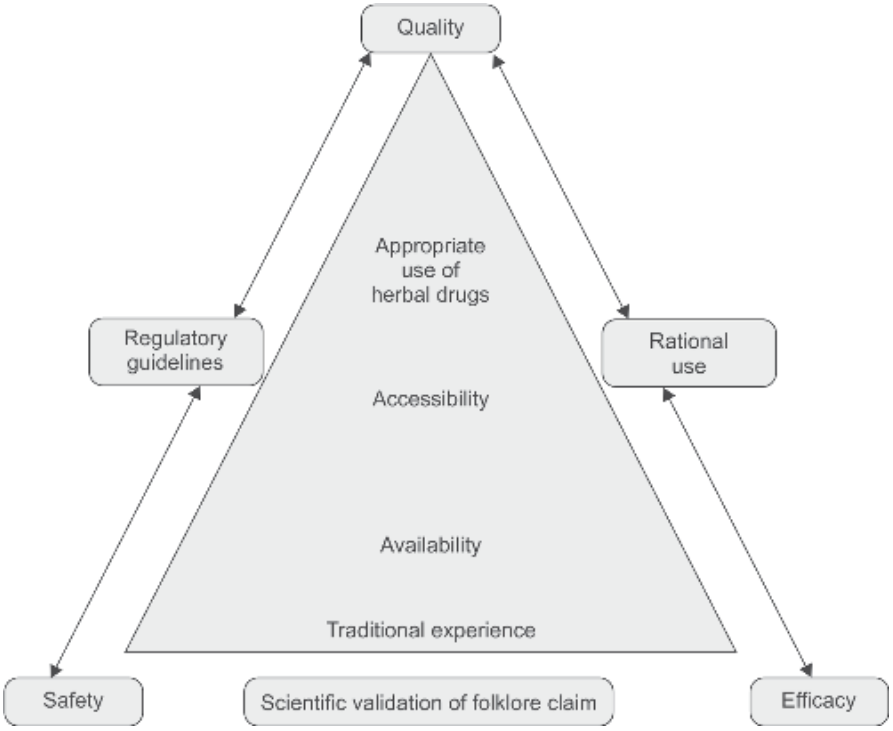


Fig. 7.1: Three pillars of herbal drugs and their rational use

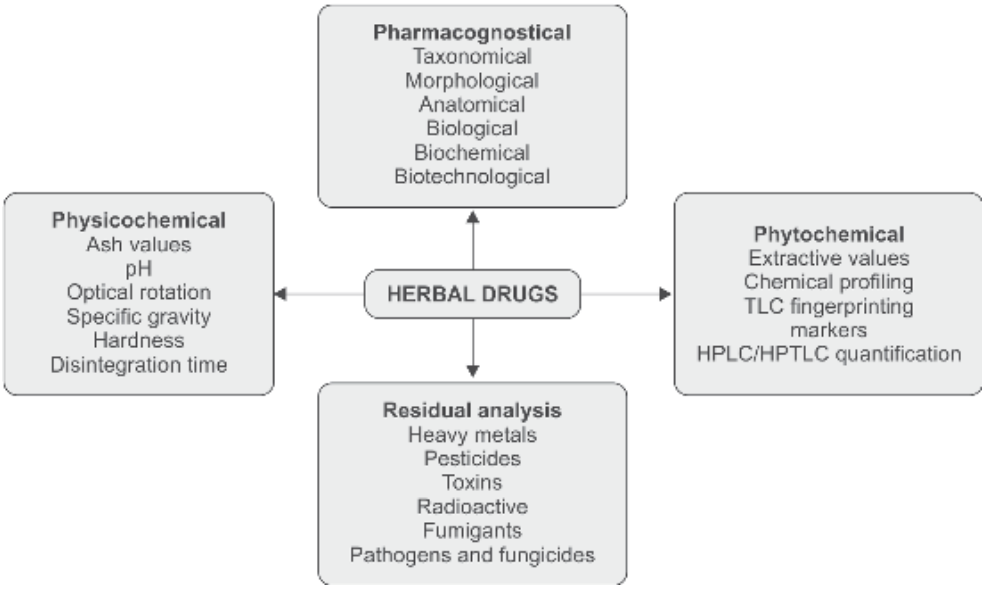


Fig. 7.2: Quality control of herbal drugs

Unit V

aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents.

11. Microbial contamination—usually medicinal plants containing bacteria and molds are coming from soil and atmosphere.

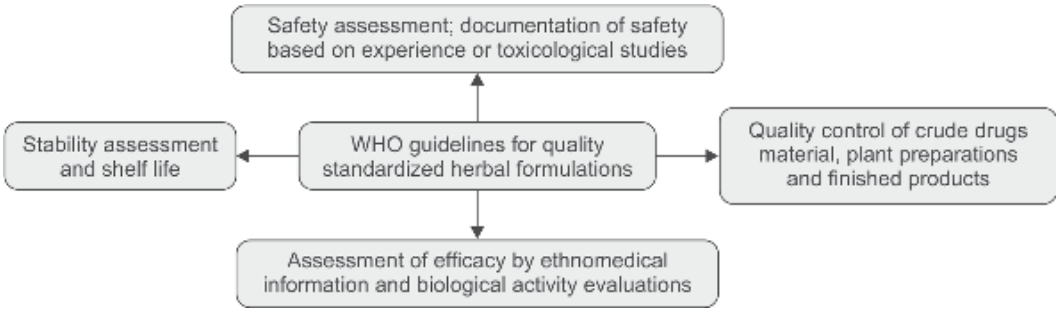

Safety assessment; documentation of safety based on experience or toxicological studies
Stability assessment and shelf life
WHO guidelines for quality standardized herbal formulations
Quality control of crude drugs material, plant preparations and finished products
Assessment of efficacy by ethnomedical information and biological activity evaluations

Fig. 7.3: WHO guidelines for quality standardized herbal formulations

Standardization of herbal formulations is essential in order to assess of quality drugs, based on the concentration of their active principles, physical, chemical, phytochemical, and standardization, and *in vitro*, *in vivo* parameters.

The quality assessment of herbal formulations is of paramount importance in order to justify their acceptability in modern system of medicine. One of the major problems faced by the herbal industry is the unavailability of rigid quality control profiles for herbal materials and their formulations.

DETERMINATION OF FOREIGN MATTER

Weigh a sample of herbal material, taking the quantity indicated above unless otherwise specified in the test procedures for the herbal material concerned. Spread it in a thin layer and sort the foreign matter into groups either by visual inspection, using a magnifying lens (6X or 10X), or with the help of a suitable sieve, according to the requirements for the specific herbal material. Sift the remainder of the sample through a No. 250 sieve; dust is regarded as mineral admixture. Weigh the portions of this sorted foreign matter to within 0.05 g. Calculate the content of each group in grams per 100 g of air-dried sample.

MACROSCOPIC AND MICROSCOPIC EXAMINATION (Fig. 7.4)

Herbs are categorized according to sensory, macroscopic and microscopic characteristics to establish, purity and possibly quality.

1. Size: Graduated ruler
2. Color: Daylight and artificial light source
3. Surface texture and fracture: Magnifying lens
4. Odor
5. Taste

Macroscopic Examination

1. ***Size:*** The measurement of length, width and thickness of herbal material is done by graduated ruler in millimetres.

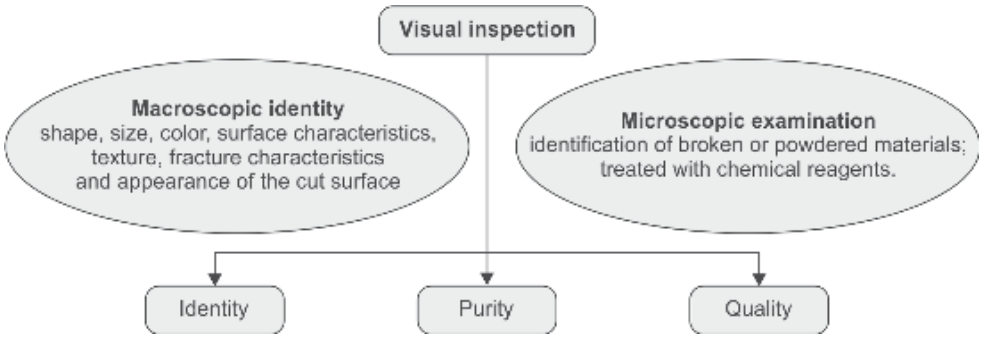

Visual inspection
Macroscopic identity
shape, size, color, surface characteristics, texture, fracture characteristics and appearance of the cut surface
Microscopic examination
identification of broken or powdered materials; treated with chemical reagents.
Identity
Purity
Quality

Fig. 7.4: Macroscopic and microscopic examination

Example: Small seeds and fruits are aligned 10 in number for the measurements on a sheet of calibrated paper, with 1 mm spacing between lines, and dividing the result by 10.

2. ***Color:*** The color of the sample is examined under daylight compared with reference sample. If required, an artificial light source with wavelengths may be used.
3. ***Surface texture and fracture characteristics:***
   a. A magnifying lens (6X to 10X) may be used to examine the untreated sample.
   b. To observe the characteristics of a cut surface wetting of sample with water or reagents can be done if required.
   c. Touch the material to determine if it is soft or hard; bend and rupture it to obtain information on brittleness and the appearance of the fracture plane whether it is fibrous, smooth, rough, granular, etc.
4. ***Odor:***
   a. If the material is expected to be innocuous, place a small portion of the sample in the palm of the hand or in a beaker of suitable size, and slowly and repeatedly inhale the air over the material. If no distinct odour is perceptible, crush the sample between the thumb and index finger or between the palms of the hands using gentle pressure.
   b. If the material is known to be dangerous, crush by mechanical means and then pour a small quantity of boiling water onto the crushed sample in a beaker.

   First, determine the strength of the odour (none, weak, distinct, strong) and then the odour sensation (aromatic, fruity, musty, mouldy, rancid, etc.). A direct comparison of the odor with a defined substance is advisable (e.g. peppermint should have an odor similar to menthol, cloves should have an odor similar to eugenol).
5. ***Taste:*** This test should be applied only if specifically required for a given herbal material.

Microscopic Examination

Microscopic identification of the herbal material is carried out with the microscope equipped with the magnification lenses, condenser, mechanical stage and objective magnification, polarizing filters, stage micrometer, and ocular micrometer. Set of drawing attachments for the microscope, a micro burner (Bunsen type), slides and cover-glasses of standard size and botanical dissecting instruments.

Preliminary Treatment Before Microscopy

1. Selection of sample
2. Softening of dried parts of herbal plant by being placed in a moist atmosphere or by soaking in water.
   a. The procedure for **softening small quantities of material** is to use a test-tube, place a wad of cotton-wool moistened with water into the bottom of a test-tube and cover with a piece of filter paper; allow it to stand overnight or until the material is soft and suitable for cutting.
   b. The procedure for **softening** for larger quantities of material, use of desiccators placing water into the lower part instead of the drying agent.
3. Softening of bark, wood and other dense and hard materials usually need to be soaked in water or in equal parts of water, ethanol and glycerol for a few hours or overnight until they are soft enough to be cut. Sometimes boiling in water for a few minutes may be required.

Preparation of Specimens for Microscopy

1. ***Powdered materials:***
   a. On a glass slide place one or two drops of water, glycerol/ethanol TS or chloral hydrate TS.
   b. Moisten the tip of a needle with water and dip into the powder.
   c. Transfer a small quantity of the material that adheres to the needle tip into the drop of fluid on the slide.

d. Stir thoroughly, and apply a cover-glass.
e. Press lightly on the cover-glass with the handle of the needle, and remove excess fluid from the margin of the cover-glass with a strip of filter-paper.

2. ***Surface tissues of leaves and flowers***

Thin leaves transparent:

a. To clarify leaves and to render pieces of thin leaves transparent, boil them directly on a slide.
b. Cut a piece of leaf into two portions, turn one piece upper side down and add chloral hydrate TS.
c. Boil the specimen carefully over a small flame of a microburner and, as soon as bubbles escape, remove the slide from the flame.
d. When the bubbles have ceased to appear, boil again until the fragments are transparent

For slightly thicker but still papery leaves,

a. Cut square pieces, about 6 mm from the edge of the leaf, if not otherwise specified.
b. The pieces should be taken one-third to one-half of the way from the leaf-base and should include a midrib or large vein.
c. In addition, cut 1 or 2 pieces from the edge including 1 or 2 indentations, where appropriate.

Place the fragments in a test-tube containing chloral hydrate TS and boil for a few minutes until they become transparent. Transfer a fragment to a slide and cut it into two equal portions. Turn one piece upper side down and align the two pieces so that both upper and lower surfaces can be observed under the microscope. Add 1–2 drops of chloral hydrate TS and apply a cover-glass. For thicker leaves, that do not become transparent enough when prepared by the method described above, clarify fragments by boiling with chloral hydrate TS in a test-tube. Transfer a fragment onto a slide, cut it into two equal portions and turn one portion upper side down. Scrape the surface of the two portions using a scalpel until only a single layer of epidermis remains. Wash the epidermis with drops of chloral hydrate TS or glycerol/ethanol TS to remove any residues. If possible, turn both parts of the epidermis upper side down, and add one of the above fluids. For very thick or fleshy leaves, pull off the upper and lower parts of epidermis by winding the softened leaf around the index finger, pressing with the thumb and the middle finger against the index finger and carefully incising, catching the incised part with forceps, and carefully bending the epidermis backwards. Petals and sepals of flowers may be treated in a similar manner.

Sections

Select representative pieces of the material being examined and cut into suitable lengths, one end of which is softened and smoothed. Prepare cross or transverse sections by cutting with a razor blade or microtome at a right angle to the longitudinal axis of the material. Prepare longitudinal sections by cutting in parallel with the longitudinal axis, either in a radial direction (radial section) or in a tangential direction (tangential section).

a. Thick materials, such as wood, woody stems, rhizomes and roots can be cut by holding the softened material between the thumb and index finger, supported by the middle finger or by holding it in the central hole of a hand microtome.
b. Thin materials such as leaves, petals and slender stems should be bound between two halves of a piece of elder-pith or other suitable support. If necessary, moisten the surface to be cut and the blade with ethanol (~375 g/l) TS. Cut the sections as thinly and evenly as possible. Transfer the sections with a brush moistened with ethanol (~150 g/l) TS to a dish containing ethanol (~150 g/l) TS. Select satisfactory sections for the preparation of the slides. For certain materials a sliding microtome may be used.
c. Seeds and fruits that are very flat, or that are small and spherical, and cannot be held in the manner described above may be

Table 7.1: Reagents with properties and uses

S. No.	Reagents	Properties	Uses
1.	*Chloral hydrate TS*	Refractive index (nD 20) of 1.44–1.48	On gentle heating chloral hydrate TS dissolves starch grains, aleurone grains, plastids, and volatile oils, and expands collapsed and delicate tissue without causing any undue swelling of cell walls or distortion of the tissues. It is the best reagent for rendering calcium oxalate clearly evident and is particularly useful for small crystals.
2.	*Lactochloral TS*	Lactochloral TS has a similar use to chloral hydrate TS	It is usually applied to sections that are difficult to clarify. It may be used cold. Before use, any air present in the specimen should be removed by placing in a desiccator and applying a vacuum.
3.	*Lactophenol TS*	Lactophenol TS may be used cold or with heating. It has a refractive index (nD 20) of 1.44	It is useful for the preparation of fungi, pollen grains, most non-oily powders, and parasites such as mites and nematode worms. This reagent dissolves calcium carbonate deposits with a slow effervescence, owing to the presence of lactic acid.
4.	*Sodium hypochlorite TS*	The bleached sections give a negative reaction to lignin	Sodium hypochlorite TS is used for bleaching deeply coloured sections. Immerse the sections in the solution for a few minutes until sufficiently bleached, wash with water and prepare the mount with glycerol/ethanol TS.
5.	*Xylene R and light petroleum R*	Solvents for fats and oils	It is used to remove fats and oils from oily powders or sections.

inserted into a notch cut into a small rubber stopper or embedded in hard paraffin (paraffin wax) as follows.

Prepare a hard paraffin block, rectangular in shape, measuring about 7 × 7 × 15 mm, and melt a small hole in the centre of one end using a heated needle or thin glass rod. Press the material, which should be dry or softened by exposure to moisture, into this hole. Then prepare sections with a microtome.

For slightly thicker but still papery leaves, cut square pieces, about 6 mm from the edge of the leaf, if not otherwise specified. The pieces should be taken one-third to one-half of the way from the leaf-base and should include a midrib or large vein. In addition, cut 1 or 2 pieces from the edge including 1 or 2 indentations, where appropriate. For broken or cut leaves take suitable fragments as described above. Place the fragments in a test-tube containing chloral hydrate TS and boil for a few minutes until they become transparent. Transfer a fragment to a slide and cut it into two equal portions. Turn one piece upper side down and align the two pieces so that both upper and lower surfaces can be observed under the microscope. Add 1–2 drops of chloral hydrate TS and apply a cover-glass.

For thicker leaves, that do not become transparent enough when prepared by the method described above; clarify fragments by boiling with chloral hydrate TS in a test-tube. Transfer a fragment onto a slide, cut it into two equal portions and turn one portion upper side

down. Scrape the surface of the two portions using a scalpel until only a single layer of epidermis remains. Wash the epidermis with drops of chloral hydrate TS or glycerol/ethanol TS to remove any residues. If possible, turn both parts of the epidermis upper side down, and add one of the above fluids. For very thick or fleshy leaves, pull off the upper and lower parts of epidermis by winding the softened leaf around the index finger, pressing with the thumb and the middle finger against the index finger and carefully incising, catching the incised part with forceps, and carefully bending the epidermis backwards. Petals and sepals of flowers may be treated in a similar manner.

Sections

Select representative pieces of the material being examined and cut into suitable lengths, one end of which is softened and smoothed. Prepare cross or transverse sections by cutting with a razor blade or microtome at a right angle to the longitudinal axis of the material. Prepare longitudinal sections by cutting in parallel with the longitudinal axis, either in a radial direction (radial section) or in a tangential direction (tangential section). Thick materials, such as wood, woody stems, rhizomes and roots can be cut by holding the softened material between the thumb and index finger, supported by the middle finger or by holding it in the central hole of a hand microtome. Thin materials such as leaves, petals and slender stems should be bound between two halves of a piece of elder-pith or other suitable support. If necessary, moisten the surface to be cut and the blade with ethanol (~375 g/l) TS. Cut the sections as thinly and evenly as possible. Transfer the sections with a brush moistened with ethanol (~150 g/l) TS to a dish containing ethanol (~150 g/l) TS. Select satisfactory sections for the preparation of the slides. For certain materials a sliding microtome may be used.

Seeds and fruits that are very flat, or that are small and spherical, and cannot be held in the manner described above may be inserted into a notch cut into a small rubber stopper or embedded in hard paraffin (paraffin wax) as follows. Prepare a hard paraffin block, rectangular in shape, measuring about 7 × 7 × 15 mm, and melt a small hole in the centre of one end using a heated needle or thin glass rod. Press the material, which should be dry or softened by exposure to moisture, into this hole. Then prepare sections with a microtome.

HISTOCHEMICAL DETECTION OF CELL WALLS AND CONTENTS

Reagents can be applied to a powdered sample or a section on a slide by the following methods: Add drops of the reagent to the sample and apply a cover-glass, then irrigate using a strip of filter-paper as described below.

Place drops of the reagent on one edge of the cover-glass of a prepared specimen. Place a strip of filter-paper at the opposite edge of the cover-glass to remove the fluid under the cover-glass by suction, causing the reagent to flow over the specimen.

Using the second method, the progress of the reaction may be observed under a microscope. Care should be taken to avoid using reagents or vapours that could attack the lenses or stages of the microscope.

Disintegration of Tissues

Cut the material into small pieces about 2 mm thick and 5 mm long, or into slices about 1 mm thick (tangential longitudinal sections are preferred for woods or xylem from stems). Use one of the following methods depending on the nature of the cell walls. For tissues with lignified cell walls use either method 1 or method 2. For tissues where lignified cells are few or occur in small groups, use method 3.

Method 1. Nitric Acid and Potassium Chlorate

Place the material in a test-tube containing about 5 ml of nitric acid (~500 g/l) TS and heat to boiling. Add a small quantity of powdered potassium chlorate R and allow to react, warming gently if necessary to maintain a

Table 7.2: Techniques of histochemical detection

S. No.	Particulars	Method
1.	*Cellulose cell walls*	Add 1–2 drops of iodinated zinc chloride TS and allow to stand for a few minutes; alternatively, add 1 drop of iodine (0.1 mol/l) VS, allow to stand for 1 minute, remove excess reagent with a strip of filter-paper and add 1 drop of sulfuric acid (~1160 g/l) TS; cellulose cell walls are stained blue to blue-violet. On the addition of 1–2 drops of cuoxam TS, the cellulose cell walls will swell and gradually dissolve.
2.	*Lignified cell walls*	Moisten the powder or section on a slide with a small volume of phloroglucinol TS and allow to stand for about 2 minutes or until almost dry. Add 1 drop of hydrochloric acid (~420 g/l) TS and apply a cover-glass; lignified cell walls are stained pink to cherry red.
3.	*Suberized or cuticular cell walls*	Add 1–2 drops of sudan red TS and allow to stand for a few minutes or warm gently; suberized or cuticular cell walls are stained orange-red or red.
4.	*Aleurone grains*	Add a few drops of iodine/ethanol TS; the aleurone grains will turn yellowish brown to brown. Then add a few drops of ethanolic trinitrophenol TS; the grains will turn yellow. Add about 1 ml of mercuric nitrate TS and allow to dissolve; the color of the solution turns brick red. If the specimen is oily, render it fat-free by immersing and washing it in an appropriate solvent before carrying out the test.
5.	*Calcium carbonate*	Crystals or deposits of calcium carbonate dissolve slowly with effervescence when acetic acid (~60 g/l) TS or hydrochloric acid (~70 g/l) TS is added.
6.	*Calcium oxalate*	Crystals of calcium oxalate are insoluble in acetic acid (~ 60g/l) TS but dissolve in hydrochloric acid (~70 g/l) TS without effervescence (if applied by irrigation the acid should be more concentrated); they also dissolve in sulfuric acid (~350 g/l) TS, but needle-shaped crystals of calcium sulfate separate on standing after about 10 minutes. In polarized light, calcium oxalate crystals are birefringent. Calcium oxalate is best viewed after the sample has been clarified (e.g. with chloral hydrate TS).
7.	*Fats, fatty oils, volatile oils and resins*	Add 1–2 drops of sudan red TS and allow to stand for a few minutes or heat gently, if necessary. The fatty substances are stained orange-red to red. Irrigate the preparation with ethanol (~750 g/l) TS and heat gently; the volatile oils and resins dissolve in the solvent, while fats and fatty oils (except castor oil and croton oil) remain intact.
8.	*Hydroxyanthraquinones*	Add 1 drop of potassium hydroxide (~55 g/l) TS; cells containing 1,8-dihydroxyanthraquinones are stained red.
9.	*Inulin*	Add 1 drop each of 1-naphthol TS and sulfuric acid (~1760 g/l) TS; spherical aggregations of crystals of inulin turn brownish red and dissolve.
10.	*Mucilage*	Add 1 drop of Chinese ink TS to the dry sample; the mucilage shows up as transparent, spherically dilated fragments on a black background. Alternatively, add 1 drop of thionine TS to the dry sample, allow to stand for about 15 minutes, then wash with ethanol (~188 g/l) TS; the mucilage turns violet-red (cellulose and lignified cell walls are stained blue and bluish violet respectively).
11.	*Starch*	Add a small volume of iodine (0.02 mol/l) VS; a blue or reddish blue color is produced. Alternatively, add a small volume of glycerol/ethanol TS and examine under a microscope with polarized light; birefringence is observed giving a Maltese cross effect with the arms of the cross intersecting at the hilum.
12.	*Tannin*	Add 1 drop of ferric chloride (50 g/l) TS; it turns bluish black or greenish black.

slight effervescence; add fresh quantities of powdered potassium chlorate R as needed. When the tissue appears to be almost completely bleached and shows a tendency to disintegrate, apply pressure with a glass rod to the material. If the material breaks, interrupt the reaction by pouring the contents of the test-tube into water. Allow the material to settle, decant it and wash it with fresh water until the acidity is removed. Transfer the material onto a slide and tease it out with a needle. Add 1 drop of glycerol/ethanol TS and apply a cover-glass. The disintegrated material gives a negative reaction for lignin.

Method 2. Nitric Acid and Chromic Acid

Place the material in a small dish and heat with nitro-chromic acid TS until the material breaks easily when pressure is applied with a glass rod. Wash the material repeatedly with water and transfer onto a slide. Tease out the material, add 1 drop of glycerol/ethanol TS and apply a cover-glass. The disintegrated material gives a negative reaction for lignin.

This treatment can also be carried out on a slide. Place a moderately thick section of the material on a slide, add the reagent and allow it to stand for about 20 minutes. Separate the cells by applying gentle pressure, or with a sliding movement of the cover-glass. This process is especially useful when the disintegration of the tissues of a section under the microscope needs to be observed to ascertain where isolated cells come from.

Method 3. Caustic Alkali Method

Place the material in a test-tube containing about 5 ml of potassium hydroxide (~110 g/l) TS or sodium hydroxide (~80 g/l) TS, and heat on a water-bath for 15–30 minutes until a portion breaks easily when pressure is applied with a glass rod. Decant the liquid and wash the softened material several times with fresh quantities of water. This method is particularly useful for the disintegration of bark, seeds, leaves and flowers, facilitating the elimination of fibres, scleroids, lactiferous tissues and epidermis. The disintegrated material gives a negative reaction for lignin.

LEAF STOMATA

Stomata are specialized cells which respond to environmental and endogenous signals and change shape to allow gas exchange. The cells are structurally adapted for movement that occurs as the result of increasing osmotic potential and turgor pressure.

Types of Stomata

In the mature leaf, four significantly different types of stoma are distinguished by their form and the arrangement of the surrounding cells, especially the subsidiary cells, as follows:

i. Anomocytic *or ranunculaceous* (irregular-celled) type: The stoma is surrounded by a definite number of cells that are not different from the remainder of the epidermis.
ii. Anisocytic *or cruciferous* (unequal celled) type: The stoma is surrounded by three cells of which one is distinctly smaller than the other two.
iii. Diacytic *or caryophyllaceous* (cross-celled) type: The stoma is enclosed by a pair of subsidiary cells whose common wall is at right angles to the guard cells.
iv. Paracytic *or rubiaceous* (parallel celled) type: The stoma is accompanied on either side by one or more subsidiary cells parallel to 30 the long axis of the pore and guard cells.

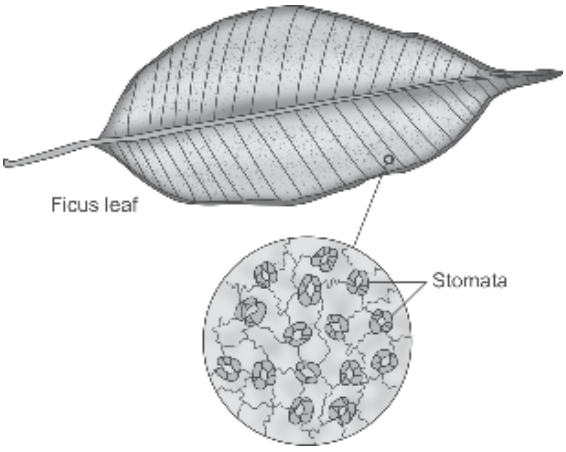


Fig. 7.5: Leaf stomata

DETERMINATION OF THE STOMATAL INDEX

a. ***Clearing of leaves:*** In a test tube containing about 5 ml of chloral hydrate TS place 5×5 mm fragments of leaves. Heat it on a water-bath for approx 15 minutes or until the fragments turned transparent.
b. ***Mounting:*** Transfer a transparent fragment to a slide; to prevent material from drying place a small drop of glycerol/ethanol TS at one side of the cover-glass.
c. Examine under a microscope with a 40X objective and a 6X eyepiece, equipped with a drawing apparatus. Mark on the drawing paper a cross (*x*) for each epidermal cell and a circle (*o*) for each stoma.
   Calculate the stomatal index as follows:
   It is the average number of **stomata** per square mm of the epidermis of the leaf. **Stomatal index** is the percentage which the number of **stomata** forms to the total number of epidermal cells, each **stomata** being counted as one cell.

$$\text{Stomatal index} = \frac{S \times 100}{E + S}$$

   where S = the number of stomata in a given area of leaf;
   E = the number of epidermal cells (including trichomes) in the same area of leaf.

Thin Layer Chromatography

Thin layer chromatography (TLC) is a chromatography technique used to separate mixtures and particularly valuable for the qualitative determination of small amounts of impurities. As it is effective and easy to perform, and the equipment required is inexpensive, the technique is frequently used for evaluating herbal materials and their preparations. It involves a stationary phase consisting of a thin layer of adsorbent material, usually silica gel, aluminum oxide, or cellulose immobilized onto a flat, inert carrier sheet. A liquid phase consisting of the solution to be separated is then dissolved in an appropriate solvent and is drawn up the plate via capillary action, separating the experimental solution based on the polarity of the components of the compound.

Principle

TLC has been included under both adsorption and partition chromatography. As different materials of different adsorptive power are used in TLC, the separation of components is not always by adsorption phenomenon. Separation may result due to adsorption and partition or by both phenomenon depending upon the nature of adsorbents used plates and solvent system used for developments.

Advantages

TLC has following advantages over paper chromatography:
a. Greater speed
b. Greater sensitivity for many substances than paper
c. Small sample requirement
d. Usually sharper preparation
e. Different kinds of reagents can be applied without damaging the plate
f. Require very little equipment
g. Require very little time
h. Spraying with corrosive solvent for identification is also permitted
i. The individual samples do not get diffuse
j. Separated component can be easily recovered.

The following parameters should be determined for the analysis of each individual herbal material:
a. Type of adsorbent and method of activation (heat at 110°C for 30 minutes);
b. Method of preparation and concentration of the test and reference solutions;
c. Volume of the solutions to be applied on the plate;
d. Mobile phase and the distance of migration;
e. Drying conditions (including temperature) and method of detection;
f. For the spots obtained: number and approximate position (or the *R*f values if necessary), and fluorescence and colour.

TLC BASIC OPERATIONS (Fig. 7.6)

A small spot of solution containing the sample is applied to a plate, about 1 cm from the base. The plate is then dipped into a suitable solvent, such as ethanol or water, and placed in a sealed container. The solvent moves up the plate by capillary action and meets the sample mixture, which is dissolved and is carried up the plate by the solvent. Different compounds in the sample mixture travel at different rates due to the differences in their attraction to the stationary phase, and because of differences in solubility in the solvent.

Plate Preparation

TLC plates are made by mixing the adsorbent, such as silica gel, with a small amount of inert binder like calcium sulfate (gypsum) and water. This mixture is spread as thick slurry on an unreactive carrier sheet, usually glass, thick aluminum foil, or plastic, and the resultant plate is dried and activated by heating in an oven for thirty minutes at 110°C. The thickness of the adsorbent layer is typically around 0.1–0.25 mm for analytical purposes and around 1–2 mm for preparative TLC.

Analysis

As the chemicals being separated may be colorless, several methods exist to visualize the spots:

- Often a small amount of a fluorescent compound, usually manganese-activated zinc silicate, is added to the adsorbent that allows the visualization of spots under a blacklight (UV_{254}).
- Iodine vapors are a general unspecific color reagent
- Specific color reagents exist into which the TLC plate is dipped or which are sprayed onto the plate.

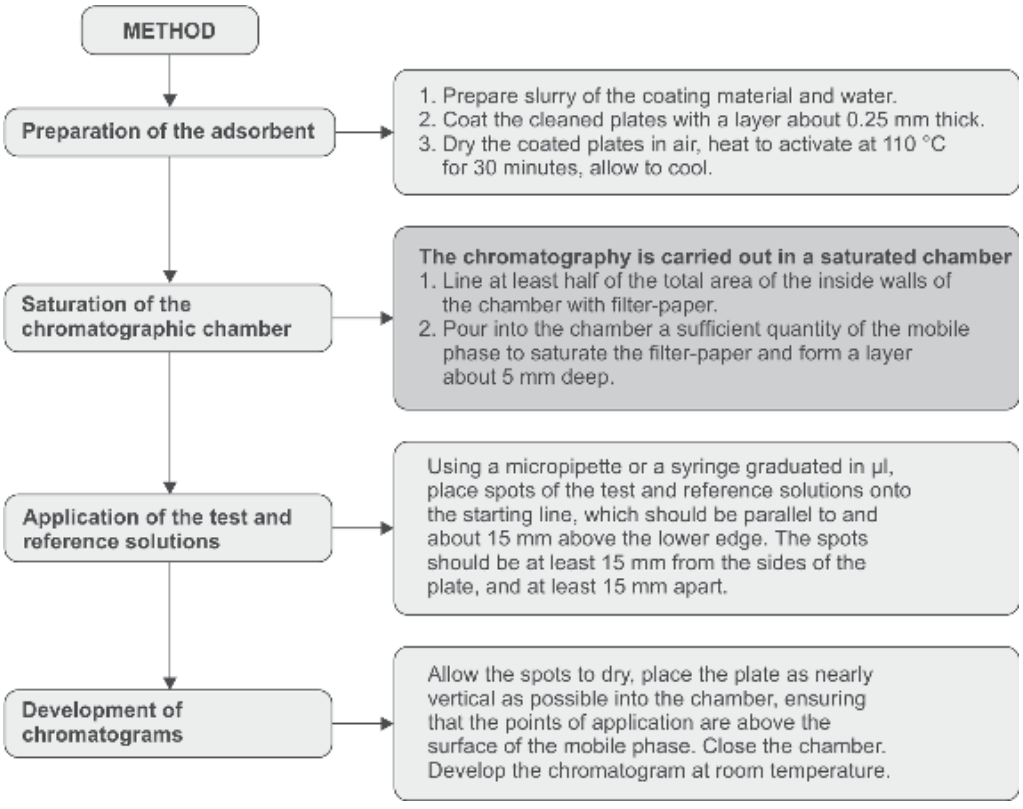

METHOD
Preparation of the adsorbent
1. Prepare slurry of the coating material and water.
2. Coat the cleaned plates with a layer about 0.25 mm thick.
3. Dry the coated plates in air, heat to activate at 110 °C for 30 minutes, allow to cool.
Saturation of the chromatographic chamber
The chromatography is carried out in a saturated chamber
1. Line at least half of the total area of the inside walls of the chamber with filter-paper.
2. Pour into the chamber a sufficient quantity of the mobile phase to saturate the filter-paper and form a layer about 5 mm deep.
Application of the test and reference solutions
Using a micropipette or a syringe graduated in µl, place spots of the test and reference solutions onto the starting line, which should be parallel to and about 15 mm above the lower edge. The spots should be at least 15 mm from the sides of the plate, and at least 15 mm apart.
Development of chromatograms
Allow the spots to dry, place the plate as nearly vertical as possible into the chamber, ensuring that the points of application are above the surface of the mobile phase. Close the chamber. Develop the chromatogram at room temperature.

Fig. 7.6: Basic operations for TLC

Development of Chromatograms

Allow the spots to dry, place the plate as nearly vertical as possible into the chamber, ensuring that the points of application are above the surface of the mobile phase. Close the chamber.

ASH VALUES (Figs 7.7 and 7.8)

The ash residue after ignition/incineration of herbal materials is determined by three different methods which measure total ash, acid-insoluble ash and water-soluble ash.

1. The *total ash* method is designed to measure the total amount of material remaining after ignition. This includes both "physiological ash", which is derived from the plant tissue itself, and "non-physiological" ash, which is the residue of the extraneous matter (e.g. sand and soil) adhering to the plant surface.
2. *Acid-insoluble ash* is the residue obtained after boiling the total ash with dilute hydrochloric acid, and igniting the remaining insoluble matter. This measures the amount of silica present, especially as sand and siliceous earth.
3. *Water-soluble ash* is the difference in weight between the total ash and the residue after treatment of the total ash with water.

Water-soluble Ash

To the crucible containing the total ash, add 25 ml of water and boil for 5 minutes. Collect the insoluble matter in a sintered-glass crucible or on an ashless filter paper. Wash with hot water and ignite in a crucible for 15 minutes at a temperature not exceeding 450°C. Subtract the weight of this residue in mg from the weight of total ash. Calculate the content of water-soluble ash in mg per g of air-dried material.

DETERMINATION OF EXTRACTABLE MATTER

This method determines the amount of active constituents extracted with solvents from a given amount of herbal material. It is employed for materials for which as yet no suitable chemical or biological assay exists.

i. ***Water soluble extractives:*** 5 g of dried drug will be, coarsely powdered, and macerated with 100 ml of water in a closed flask for 24 hr, shaking frequently during the first 6 hr and will be allowing to stand for 18 hr, then it will be rapidly filtered and the 25 ml of filterate will be evaporated to dryness in a tared flat-bottomed shallow dish. Then it will be dried at 105°C and weighed. The percentage of water-soluble extractive with reference to air dried drug will be calculated.

ii. ***Alcohol-soluble extractives:*** 5 g dried drug, will be coarsely powdered, and macerated with 100 ml of ethanol of specified strength in a closed flask for 24 hr, shaking frequently during the first 6 hr and allowing to stand for 18 hr thereafter, it will be filtered rapidly taking precaution against loss of ethanol, and evaporated to 25 ml of the filterate to dryness in a tared flat-bottomed shallow dish, then it will be dried at 105°C and weighed. The percentage of ethanol-soluble extractive with reference to air dried drug will be calculated.

The percentage yield of each extract was calculated by using the following formula:

Percentage yield

$$= \frac{\text{Weight of extract}}{\text{Weight of powder drug taken}} \times 100$$

DETERMINATION OF WATER AND VOLATILE MATTER

An excess of water in herbal materials will encourage microbial growth, the presence of fungi or insects, and deterioration following hydrolysis. Limits for water content should therefore be set for every given herbal material. This is especially important for materials that absorb moisture easily or deteriorate quickly in the presence of water.

The test for *loss on drying* determines both water and volatile matter. Drying can be carried out either by heating to 100–105°C or in a desiccator over phosphorus pentoxide R under atmospheric or reduced pressure at room temperature for a specified period of

DETERMINATION OF ASH

Total Ash

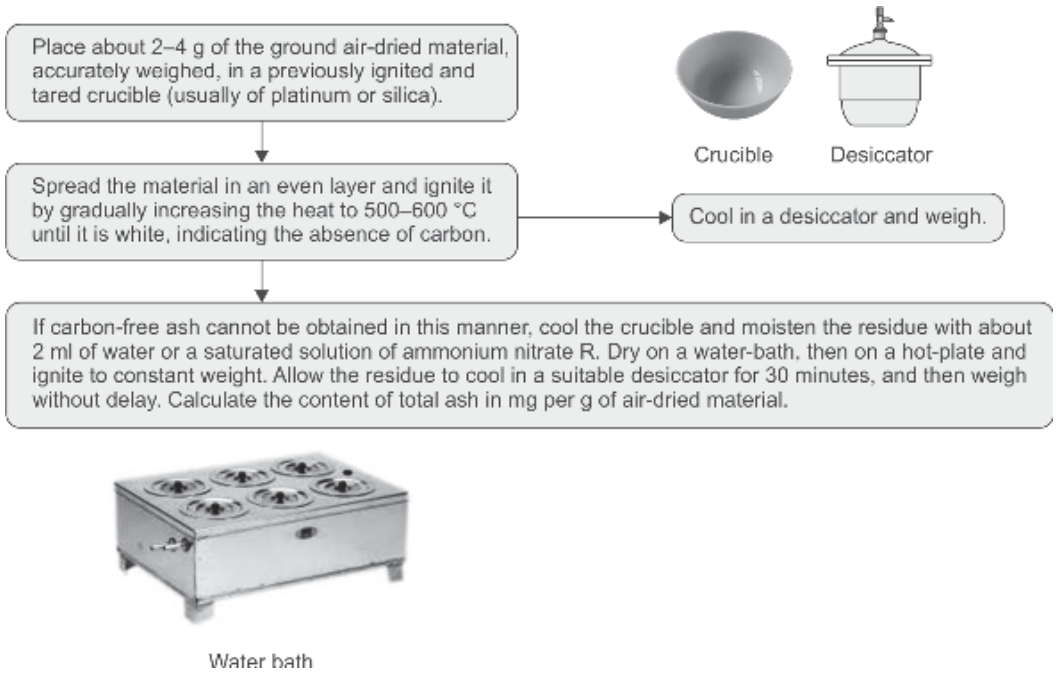

Place about 2–4 g of the ground air-dried material, accurately weighed, in a previously ignited and tared crucible (usually of platinum or silica).
Crucible
Desiccator
Spread the material in an even layer and ignite it by gradually increasing the heat to 500–600 °C until it is white, indicating the absence of carbon.
Cool in a desiccator and weigh.
If carbon-free ash cannot be obtained in this manner, cool the crucible and moisten the residue with about 2 ml of water or a saturated solution of ammonium nitrate R. Dry on a water-bath, then on a hot-plate and ignite to constant weight. Allow the residue to cool in a suitable desiccator for 30 minutes, and then weigh without delay. Calculate the content of total ash in mg per g of air-dried material.
Water bath

Fig. 7.7: Determination of total ash

Acid-insoluble Ash

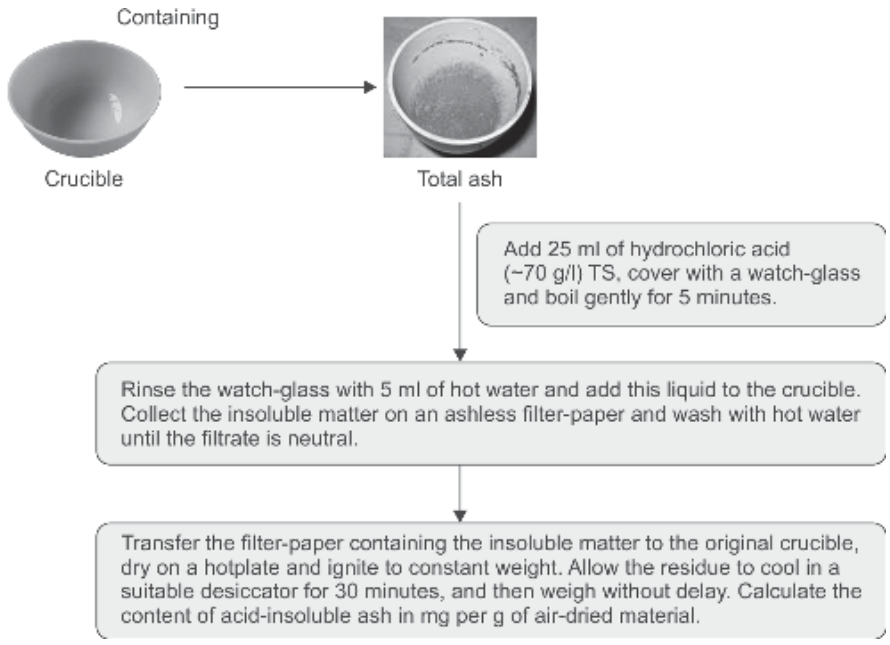

Containing
Crucible
Total ash
Add 25 ml of hydrochloric acid (~70 g/l) TS, cover with a watch-glass and boil gently for 5 minutes.
Rinse the watch-glass with 5 ml of hot water and add this liquid to the crucible. Collect the insoluble matter on an ashless filter-paper and wash with hot water until the filtrate is neutral.
Transfer the filter-paper containing the insoluble matter to the original crucible, dry on a hotplate and ignite to constant weight. Allow the residue to cool in a suitable desiccator for 30 minutes, and then weigh without delay. Calculate the content of acid-insoluble ash in mg per g of air-dried material.

Fig. 7.8: Determination of acid-insoluble ash

time. The desiccation method is especially useful for materials that melt to a sticky mass at elevated temperatures.

DETERMINATION OF VOLATILE OILS

Volatile oils are characterized by their odour, oil-like appearance and ability to volatilize at room temperature. Chemically, they are usually composed of mixtures of, for example, monoterpenes, sesquiterpenes and their oxygenated derivatives. Aromatic compounds predominate in certain volatile oils. Because they are considered to be the "essence" of the herbal material, and are often biologically active, they are also known as "essential oils". The term "volatile oil" is preferred because it is more specific and describes the physical properties. Figure 7.9 depicts determination of volatile oils.

Procedure

A. Method A: This method is used to determine the volatile oils with relative density less than 1.0.

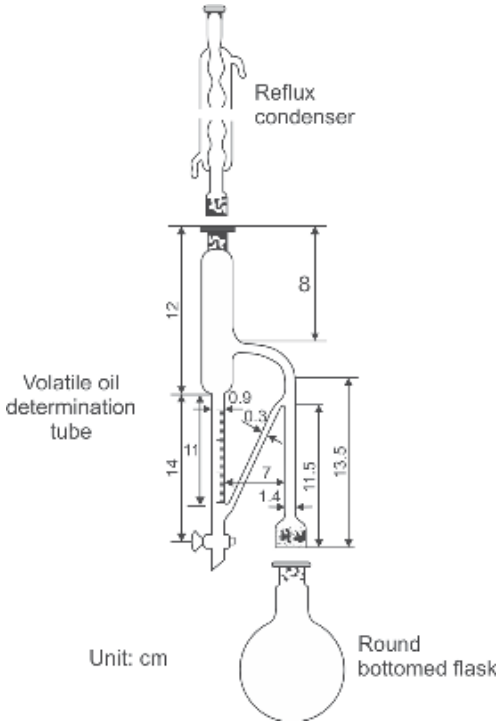


Fig. 7.9: Determination of volatile oils

Take a quantity of the powdered sample which is expected to give 0.5–1.0 ml of volatile oil, weigh accurately to the nearest 0.01 g, and put into a round-bottomed flask. Add 300–500 ml of water (or appropriate amount) and a few glass beads, shake and mix well. Connect the round bottomed flask to a volatile oil determination tube and then connect the volatile oil determination tube to a reflux condenser. Add water through the top of reflux condenser until the graduated tube of volatile oil determination tube is filled and overflows to the round-bottomed flask. Heat the flask gently until boiling by using an electric heating jacket or other appropriate means. Continue the gentle boiling for about 5 h until the volume of oil does not increase. Stop heating; allow it to stand for a while. Open the stopcork at the lower part of volatile oil determination tube and run off the water layer slowly until the oily layer is 5 mm above the zero mark. Allow to stand for at least 1 h, open the stopcock again, run off the remaining water layer carefully until the oily layer is just on the zero mark. Record the volume of oil in the graduated tube of volatile oil determination tube and calculate the percentage of volatile oil in sample.

B. Method B: This method is used to determine the volatile oils with relative density more than 1.0.

Add 300 ml of water and a few pieces of glass beads into a round-bottomed flask. Connect the round-bottomed flask to volatile oil determination tube. Add water through the top of volatile oil determination tube until the graduated tube is filled and overflows to the round-bottomed flask. Add 1 ml of xylene by using a pipette and then connect the reflux condenser to volatile oil determination tube. Heat the flask until boiling, continue the heating to allow the distillation proceed at a rate that will keep the middle part of the condenser cold. Stop heating after 30 min, and allow it to stand for at least 15 min. Record the volume of xylene in the graduated tube of volatile oil determination tube. Carry out the

procedure as described in Method A beginning at the words "Take a quantity of the powdered sample". Subtract the volume of xylene previously observed from the volume of oily layer, the difference in volume is taken to be the content of volatile oil, calculate the percentage of volatile oil in sample.

DETERMINATION OF BITTERNESS VALUE

Bitter substances are mostly composed of two or more constituents with various degrees of bitterness, it is first necessary to measure total bitterness by taste. Herbal materials that have a strong bitter taste ("bitters") are therapeutically used as appetizing agents. Their bitterness stimulates secretions in the gastrointestinal tract, especially of gastric juice.

Method

1. After rinsing the mouth with safe drinking water, taste 10 ml of the most dilute solution swirling it in the mouth mainly near the base of the tongue for 30 seconds.
2. If the bitter sensation is no longer felt in the mouth after 30 seconds, spit out the solution and wait for 1 minute to ascertain whether this is due to delayed sensitivity.
3. Then rinse with safe drinking water.
4. The next highest concentration should not be tasted until at least 10 minutes have passed.
5. The threshold bitter concentration is the lowest concentration at which a material continues to provoke a bitter sensation after 30 seconds.
6. After the first series of tests, rinse the mouth thoroughly with safe drinking water until no bitter sensation remains.
7. Wait for at least 10 minutes before carrying out the second test. In order to save time in the second test, it is advisable to ascertain first whether the solution in tube no. 5 (containing 5 ml of *S*T in 10 ml) gives a bitter sensation. If so, find the threshold bitter concentration of the material by tasting the dilutions in tubes 1–4. If the solution in tube no. 5 does not give a bitter sensation, find the threshold bitter concentration by tasting the dilutions in tubes 6–10.
8. All solutions and the safe drinking water for mouth washing should be at 20–25°C. Calculate the bitterness value in units per g using the following formula:

$$\frac{2000 \quad c}{a \quad b}$$

where a = the concentration of the stock solution (*S*T) (mg/ml);
b = the volume of *S*T (in ml) in the tube with the threshold bitter concentration;
c = the quantity of quinine hydrochloride R (in mg) in the tube with the threshold bitter concentration

DETERMINATION OF HEMOLYTIC ACTIVITY

The most characteristic part of saponins is their ability to cause hemolysis; when added to the suspension the saponins produce change in erythrocyte membranes causing hemoglobin to diffuse into the surrounding medium.

The hemolytic activity of herbal materials, or a preparation containing saponins, is determined by comparison with that of a reference material, saponin R, which has a hemolytic activity of 1000 units per g.

A suspension of erythrocytes is mixed with equal volumes of a serial dilution of the herbal material extract. The lowest concentration to effect complete hemolysis is determined after allowing the mixtures to stand for a given period of time. A similar test is carried out simultaneously with saponin R.

Calculate the hemolytic activity of the herbal material using the following formula

$$1000 \times a/b$$

where 1000 = the defined hemolytic activity of saponin R in relation to ox blood;
a = quantity of saponin R that produces total hemolysis (g);
b = quantity of herbal material that produces total hemolysis (g).

TANNINS

Tannins (or tanning substances) are polyphenolic plant secondary metabolites substances capable of turning animal hides into leather by binding proteins to form water-insoluble substances that are resistant to proteolytic enzymes. This process, when applied to living tissue, is known as an "astringent" action and is the reason for the therapeutic application of tannins.

Determination of Tannins

1. Powder the herbal material weighed accurately, introduce into a conical flask. Add 150 ml of water and heat over a boiling water-bath for 30 minutes.
2. Cool, transfer the mixture to a 250 ml volumetric flask and dilute to volume with water.
3. Allow the solid material to settle and filter the liquid through a filter paper, diameter 12 cm, discarding the first 50 ml of the filtrate.
4. To determine the total amount of material that is extractable into water, evaporate 50.0 ml of the plant material extract to dryness, dry the residue in an oven at 105°C for 4 hours and weigh ($T1$).
5. To determine the amount of herbal material not bound to hide powder that is extractable into water, take 80.0 ml of the herbal material extract, add 6.0 g of hide powder R and shake well for 60 minutes. Filter and evaporate 50.0 ml of the clear filtrate to dryness. Dry the residue in an oven at 105°C and weigh ($T2$).
6. To determine the solubility of hide powder, take 6.0 g of hide powder R, add 80.0 ml of water and shake well for 60 minutes. Filter and evaporate 50.0 ml of the clear filtrate to dryness. Dry the residue in an oven at 105°C and weigh ($T0$).

Calculate the quantity of tannins as a percentage using the following formula:

$$\frac{[T1 - (T2 - T0)] \times 500}{w}$$

where w = the weight of the herbal material in grams.

DETERMINATION OF SWELLING INDEX

The swelling index is the volume in ml taken up by the swelling of 1 g of herbal material under specified conditions. Swelling properties of materials provide them therapeutic or pharmaceutical utility especially gums and those containing an appreciable amount of mucilage, pectin or hemicellulose.

Its determination is based on the addition of water or a swelling agent as specified in the test procedure for each individual herbal material (either whole, cut or pulverized). Using a glass-stoppered measuring cylinder, the material is shaken repeatedly for 1 hour and then allowed to stand for a required period of time.

Procedure

1. Carry out simultaneously no fewer than three determinations for any given material. Introduce the specified quantity of the herbal material concerned, previously reduced to the required fineness and accurately weighed, into a 25 ml glass-stoppered measuring cylinder.
2. The internal diameter of the cylinder should be about 16 mm, the length of the graduated portion about 125 mm, marked in 0.2 ml divisions from 0 to 25 ml in an upward direction.
3. Unless otherwise indicated in the test procedure, add 25 ml of water and shake the mixture thoroughly every 10 minutes for 1 hour.
4. Allow to stand for 3 hours at room temperature, or as specified. Measure the volume in ml occupied by the herbal material, including any sticky mucilage.
5. Calculate the mean value of the individual determinations, related to 1 g of herbal material.

DETERMINATION OF FOAMING INDEX

Many herbal plants contain saponins that can cause persistent form when aqueous decoction is shaken.

1. Weigh accurately, 1 g reduce herbal material to a coarse powder (sieve size no. 1250) and transfer to a 500 ml conical flask containing 100 ml of boiling water.
2. Maintain at moderate boiling for 30 minutes.
3. Cool and filter into a 100 ml volumetric flask and add sufficient water through the filter to dilute to volume.
4. Pour the decoction into 10 stoppered test-tubes (height 16 cm, diameter 16 mm) in successive portions of 1 ml, 2 ml, 3 ml, etc. up to 10 ml, and adjust the volume of the liquid in each tube with water to 10 ml.
5. Stopper the tubes and shake them in a lengthwise motion for 15 seconds, two shakes per second.
6. Allow to stand for 15 minutes and measure the height of the foam. The results are assessed as follows:
   a. If the height of the foam in every tube is less than 1 cm, the foaming index is less than 100.
   b. If a height of foam of 1 cm is measured in any tube, the volume of the herbal material decoction in this tube (a) is used to determine the index. If this tube is the first or second tube in a series, prepare an intermediate dilution in a similar manner to obtain a more precise result.
   c. If the height of the foam is more than 1 cm in every tube, the foaming index is over 1000. In this case repeat the determination using a new series of dilutions of the decoction in order to obtain a result. Calculate the foaming index using the following formula:

$$1000/a$$

   where a = the volume in ml of the decoction used for preparing the dilution in the tube where foaming to a height of 1 cm is observed.

DETERMINATION OF PESTICIDE RESIDUES

Determination of Total Chlorine and Phosphorus

Most pesticides contain organically bound chlorine or phosphorus.

Recommended Procedure

Preparation of samples: Reduce the herbal material to a fine powder, and extract with a mixture of water and acetonitrile R. Most pesticides are soluble in this mixture, while most cellular constituents (e.g. cellulose, proteins, amino acids, starch, fats and related compounds) are sparingly soluble and are thus removed. A number of polar and moderately polar compounds may also be dissolved; it is therefore necessary to transfer the pesticides to light petroleum R. For pesticides containing chlorine, further purification is seldom required, but for those containing phosphorus, further purification by column chromatography may be necessary, eluting with mixtures of light petroleum R and ether R.

Determination of Arsenic and Toxic Metals

Limit Test for Arsenic

Arsenic is abundant in nature and its presence in herbal materials should be no different to its wide occurrence in foods. A popular test method relies on the digestion of the herbal material matrix followed by subjection of the digestate to a comparative colorimetric test in a special apparatus. The test method described below uses colorimetry and does not use toxic mercuric bromide paper. The method uses *N*-diethylmethyldithiocarbamate in pyridine and it reacts with hydrogen arsenide to afford a red–purple complex. The limit is expressed in terms of arsenic (III) trioxide (As_2O_3).

Limit test for cadmium and lead

Limit test for total toxic metals as lead

Limit test for total toxic metals as lead in extracts

Determination of Specific Toxic Metals

Determination of Microorganisms

Total viable aerobic count: The total viable aerobic count (TVC) of the herbal material being examined is determined, as specified in the test procedure below, using one of the following methods: Membrane-filtration,

plate count or serial dilution. Aerobic bacteria and fungi (moulds and yeasts) are determined by the TVC.

Usually a maximum permitted level is set for certain products, but when the TVC exceeds this level, then it is unnecessary to proceed with determination of specific organisms; the material should be rejected without being subjected to further testing.

Determination of Aflatoxins

Tests for Aflatoxins

These tests are designed to detect the possible presence of aflatoxins B1, B2, G1 and G2, which are highly toxic contaminants in any material of plant origin.

Recommended procedure: The method described below does not require the use of toxic solvents, such as chloroform and dichloromethane. It uses a multifunctional column, which contains lipophilic and charged active sites, and high-performance liquid chromatography (HPLC) using fluorescence detection to determine aflatoxins B1, B2, G1 and G2.

Radioactive Contamination

Following a severe nuclear accident, the environment may be contaminated with airborne radioactive materials. These may deposit on the leaves of medicinal plants. Their activity concentration and the type of radioactive contamination can be measured by the radiation monitoring laboratories of most of the WHO member states. The activity concentration of radioisotopes in herbs should be assessed by the competent national radiohygiene laboratories taking into account the relevant recommendations of international organizations, such as Codex Alimentarius, the International Atomic Energy Agency (IAEA), the Food and Agriculture Organization of the United Nations (FAO) and WHO. Since radionuclides from accidental discharges vary with the type of facility involved, a generalized method of measurement is not yet available.

EFFICACY OF HERBAL MEDICINE

The efficacy of medicine is the measure of its ability to improve health and well-being. The usage of herbal remedies is often acceptable in many cases due to its long history of usage from prehistoric time. The term "efficacious" may be interpreted differently by the practitioners of traditional medicine (of which herbal medicine is a type) and the proponents of so-called modern medicine (conventional medicine).

Traditional medicine usually takes a "holistic" approach where the physical, spiritual (which includes mental), and most often social well-being of an individual are treated. Thus, the medicinal value of an herbal product may be intimately related to its nutritional and psychological aspects. WHO has defined health in terms of both physical and mental well-being. However, modern medical practice usually emphasizes only physical well-being. In recent times, the trend in the right direction is to develop more of an integrated approach of treatment involving physical, mental, and social well-being. One way to bridge the philosophical gap between these two systems (and thus to adopt more of an integrated approach) is the WHO concept of health, which emphasizes the best part of both systems. Through this "one system of medicine" we may be able to design appropriate indicators of efficacy and the practical methodology to test them. This will, however, require openness and understanding from both sides.

Assessment of Efficacy

As for conventional concepts, case reports and case series are very useful for hypothesis formulation, but they cannot be used to test the presence of a valid statistical association.

Although case series are frequently sufficiently large to permit quantification of the effect, the ability to interpret such information is severely limited by the lack of an appropriate comparison group. Randomized clinical trials take away many of these biases and

limitations that are present in the case series design. Although randomized clinical trials should be the ideal way for evaluating the efficacy of herbal drugs, it cannot always be implemented for several reasons. These trials are inherently interventional in nature, and it may be sometimes ethically questionable whether such studies can be designed without sufficient existing evidence about its efficacy and safety in animals.

For edible plants or for plants used as herbal medicines since early times by human beings, there may be an argument for conducting trials without animal experimentation, but there still remain unsolved ethical issues in this area. Numerous variables (including sociocultural factors, beliefs, and placebo effects) influencing the effectiveness and quality of herbal drugs also make it difficult to design trials on these drugs. Use of conventional protocols for chemical analysis, animal experimentation, and toxicity studies blur the demarcation between traditional and modern pharmaceutical approaches.

SAFETY OF HERBAL MEDICINE

Herbal medicines are generally regarded as safe based on their long-standing use in various cultures. However, there are case reports of serious adverse events after administration of herbal products. In a lot of cases, the toxicity has been traced to contaminants and adulteration. However, some of the plants used in herbal medicines can also be highly toxic. As a whole, herbal medicines can have a risk of adverse effects and drug–drug and drug–food interactions if not properly assessed.

The toxic effects of herbal preparation may be attributed mainly due to inherent toxicity of plant constituents and ingredients and manufacturing malpractice and contamination.

Evaluation of the toxic effects of plant constituents of herbal formulation requires detailed phytochemical and pharmacological studies. It is, however, safe to assume that, based on human experiences in various cultures, the use of toxic plant ingredients has already been largely eliminated and recent reports of toxicity could largely be due to misidentification and overdosing of certain constituents.

Contaminants in Herbal Medicine

Potential contaminants of herbal medicines include microorganisms, microbial toxins, pesticides, fumigation agents, radioactivity, and the presence of toxic compounds of toxic metals. Some of these contaminants have been identified by the committee for proprietary medicinal products (CPMP) of the European Community (EC) for use in controlling the purity of herbal medications in the European Union (EU). The CPMP guidelines highlight the need for good control of starting materials and the finished product and emphasize the importance of good manufacturing practice.

Substitution and Misidentification of Herbal Substances

Risks associated with herbal medicine products were first reported for medicinal plants of the asteraceae family, hypericin and aristolochia genus, and kava-kava. A number of cases of inadvertent or deliberate substitution of the constituents of Chinese herbal preparations are cited in the literature. For example, Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*Panax quinquefolium*), and Japanese ginseng (*Panax pseudo-ginseng*) have been substituted for Korean or Chinese ginseng (*Panax ginseng*). Sometimes the substitute has a much greater toxicity than the original material. Herbal products range from phytomedicines to food and dietary supplements where therapeutic claims are not allowed. There may be a strong connection with traditionally used herbal medicines and folkloric knowledge, which in some countries justifies less stringent regulations. Generally, there are no universal legislative criteria for use in regulating herbal products.

Documented or Regulatory Approaches

Herbal medicines were first included in the WHO International Conference on Drug Regulatory Authorities in 1986. In 1991, WHO prepared draft guidelines for assessment of herbal medicines, which were adopted by the 6th International Conference on Drug Regulatory Authorities (ICDRA). This includes basic criteria for quality, safety, and efficacy of herbal medicines. These guidelines provide valuable assistance to national regulatory authorities, scientific organizations, and manufacturers to undertake assessment of documentation of submissions. Following the recommendations of the 6th ICDRA in 1991, WHO continued to develop pharmaceutical monographs on herbal medicines on the basis of guidelines for the assessment of herbal medicines:

Part I: Botanical characteristics, major active constituents, and quality control (QC).

Part II: Summaries of clinical applications, pharmacology, precautions, and adverse reactions.

The purpose of the WHO monographs was to:

- Provide scientific information on safety, efficacy, and quality control of medicinal plants; and
- Facilitate proper use of herbal medicines.

In the United States, herbal products can only be marketed as food supplements. Specific health claims need US Food and Drug Administration (FDA) approval.

Requirements for pharmaceutical assessment that cover the safety assessment of herbal products are as follows:

- Experience of safety
- Toxicological studies, where vindicated

The risks associated with the use of herbal substances, which has unfortunately resulted in a number of fatalities, are considered highly significant and are related to problems associated with the failure of good handling and manufacturing of certain products. Lack of standardization, contamination with toxic metals, inadvertent and deliberate substitution of other herbs, and adulteration with western pharmaceuticals also contribute in associated risks. Clearly, there is a danger to the public without a proper evaluation of the possible risks which could arise from the ingestion of medicinal herbs.

Development of Monitoring and Surveillance Systems

Herbal medicinal products are classified as a drug without a therapeutic claim in many countries. A therapeutic claim means classification as a drug product and subject to drug regulations as followed in some developing countries. For the application of general health laws to herbal products, microbiological tests are used as a means to assess safety. For standardization, safety, and efficacy assessment, legislation must be introduced to ensure that required standards are met. It is, therefore, necessary to keep pace with changing consumer needs.

The evaluation of new herbal products consists of six steps, which define the following:

- Characteristics of new substances,
- History and pattern of use,
- Any adverse reaction,
- Biological action,
- Toxicity and carcinogenicity, and
- Clinical trial data.

The presence of impurities is either:

- An intended addition, or
- Accidental contamination via processing.

Assessment of Toxicity

For herbal products, analysis of the active pharmaceutical ingredients may be best approached by analysis of one or more hypothesized active ingredients, analysis of a chemical constituent that constitutes a sizeable percentage of total ingredients, and chemical fingerprinting of ingredients. Toxicity investigation will also be required because the analysis alone is unlikely to reveal the contributions to toxicity itself. In assessing toxicity of an

herbal medicine, the dose chosen is very important. Toxicity assessment involves one or more of the following techniques:

- *In vivo* techniques
- *In vitro* techniques
- Cell line techniques
- Micro-array and other modern techniques
- Standardization
- Techniques to adequately model toxicity

The issues of mixtures and deviation from conventional pharmacological approaches remain a major problem, along with the consequences of using the wrong source plants or ingredients, variable content of active constituents, and a narrow therapeutic window with herbal medicines. Concurrent contamination with any one of the toxic metals, bacteria, viruses, or pesticides may also occur.

Risk Assessment Approach

The risk assessment procedure considers the following steps in risk characterization:

- Hazard identification
- Dose–response assessment
- Exposure assessment

Risk characterization enables the estimation of any adverse effect and provides a means of devising risk management, if appropriate. Risk assessment is a process that enables management and communication tools to be developed to control any adverse effects of pesticide applications during cultivation and storage of medicinal herbs. It comprises the discrete steps of identification of source and hazard, dose response, exposure, and calculation of risk. There are acceptable risk management concepts which can be applied to public health and the environment, arising from exposure to pesticides. There are two groups at risk, namely (i) workers handling herbal products, and (ii) people using herbal products. In the risk assessment process, studies need to take into account formulation of the herbal products and their bio-availabilities. It is necessary to combine quality application data with chronic toxicity data.

CONCLUSION

The approximate licensed Herbal Pharmacies are increasing with annual turnover which accounts for nearly one-eighth of total pharmaceutical business. The existing prototype of pharmacovigilance and its associated tools have been established in relation to synthetic drugs, and applying these methods to monitoring the safety of herbal medicines presents unique challenges in addition to those described for conventional medicines. Challenges also arise from the current regulatory framework for herbal medicines in India. Several other tools used in pharmacovigilance of conventional medicines, such as prescription-event monitoring, and the use of computerized health-record databases, currently are of no use for evaluating the safety of herbal and other non-prescription medicines.

Many complex issues relating to adverse event detection with traditional products include the problems of products with multiple ingredients, drugs of multiple systems of medicine, misclassification of names, poor standardization of products, lack of clinical trials, variation in manufacturing processes, contamination, adulteration and misidentification of herbs.

In the longer term, improvements in safety monitoring of herbal medicines include modifications to existing methodology, patient reporting and greater consideration of pharmacogenetics and pharmacogenomics in optimizing the safety of herbal medicines.

CHAPTER 8

Status of Herbal Formulation

India is the largest producer of medicinal herbs and approximately called the botanical garden of the world. It is one of the most important countries in the world in terms of floristic diversity.

India has global position in the field of traditional medicines. About 90% herbal raw drugs used in the manufacture of vegetable drugs are obtained from the wild source which is limited. There are about 45,000 plants species in India which are in abundant in the regions of eastern Himalaya, western Ghats and Andman and Nicobar Islands. The rich heritage of flora is due to diversified and varied agro-climatic conditions. The official documented plants with medicinal potential are 3,000 but traditional practitioner use about 8,000 vegetable drugs.

In rural India, 70% of the population is dependent on the traditional system of medicine. Land-based developmental activities provide means of livelihood, health and opportunity for employment. India has global position in the field of traditional medicines.

Out of more than 25000 plants of medicinal value, only 10 % are used for their medicinal value. Around 1800 species are systematically documented in the codified Indian systems of medicine. These herbal products are preventive, protective, nutritive and curative. Botanically, a herb is a plant with a non-woody stem which withers and dries down after flowering. The term applies to all plants whose leaves, stems, roots, flowers, fruits and seeds have medicinal uses. There are thousands of herbs which can be processed to prepare their extracts in the form of liquid, paste and powders. As per WHO report, more than 80% of the world population use medicines made from herbal and natural products. Current global market of herbal and Ayurvedic medicines is estimated to be more than US$ 100 billion, out of this EU accounts for about 40%, Japan 20%, USA 10%. The Asian countries together account for 30% of the global market. During the last decade importance of alternative medicine was realized and with the inclination to this, the growth rate of ayurvedic and herbal industry can be put more than 30% for the last 25 years. The world, which due to technological advances, developed medicines which are quick acting, potent and capable to treat and provide symptomatic relief, has now started to feel the need for longer lasting and more fundamental cures for their problems of health. Attention now being shifted from relief to prevention and cure.

The Journey of traditional medicine to herbal formulation is mentioned in Fig. 8.1.

STATUS OF HERBAL FORMULATIONS

Herbal formulations are dosage form consisting of either combination of one or more herbs or processed herb in specified quantities to provide specific nutritional, cosmetic or other benefits meant for diagnose, treat, mitigate disease. Herbal medicinal products have become a subject of increasing global importance, for their health benefits and economic considerations. The global demand for these products is increasing due to reinsured interest of consumers in natural products, as they are considered safer and more cost-effective than synthetic counterparts.

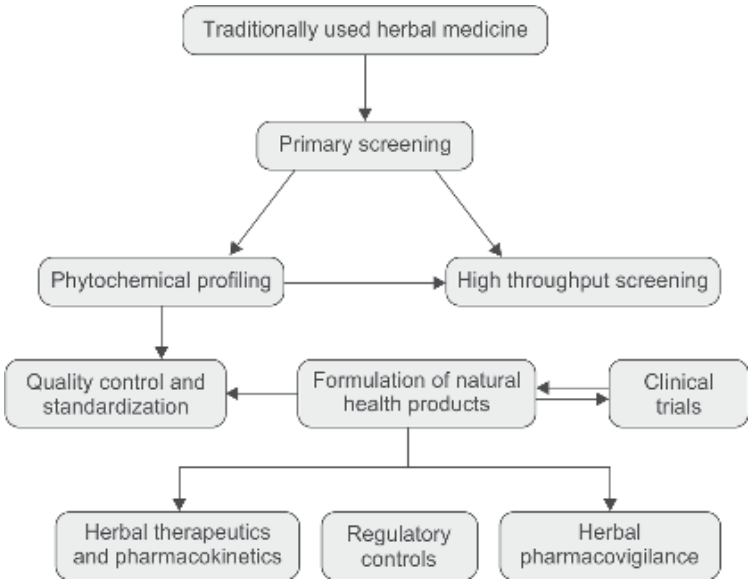


Fig. 8.1: Journey of traditional medicine to herbal formulation

According to a survey of World Health Organization (WHO) about 80 per cent of population in these countries still rely on traditional or herbal medicines for their primary healthcare needs.

Trade in medicinal plants is often unregulated in most parts of the world. Lack of species-specific records at national and international levels and practice of grouping fresh and dried medicinal plants under one broad category further complicate the problem. Furthermore, there is an insufficient information on sources of demand, dynamics of medicinal plant's trade and supply channels. The developing countries which have rich resources of biodiversity can be benefited from the present state, if the information on the major user groups and international trends in demand and supply is made available.

A large number of user groups like pharmaceutical and food industries, traditional or alternative practitioners, folk or household medicine users, cosmetic and flavour industry and many more use these plants for their medicinal, aromatic, and health giving properties. The available major groups are:

- Phytopharmaceuticals;
- Natural health products;
- Herbal medicines;
- Phyto-cosmetic and personal hygiene products.

Herbal Medicines

Herbal medicines are also referred as botanical medicines, makes use of herbs for therapeutic or medicinal purposes. It is the oldest form of healthcare known to mankind and constituted an integral part of development of modern civilization. The World Health Organization (WHO) estimates that 4 billion people of the world population presently use herbal medicines for their primary healthcare. Medicinal plants are major component of all indigenous or alternative systems of medicine. They are common element in ayurvedic, homeopathic, naturopathic, oriental and native American Indian medicine. WHO notes that about three-fourths of plant-derived drugs correlate directly with their traditional uses in native cultures.

The details of production, demand, import and pharmaceutical companies associated with phytopharmaceuticals with the trends in global market are mentioned in Tables 8.1 and 8.2.

Table 8.1: Phytopharmaceuticals

Heading	Details
Production	More than 80% of world's production of pharmaceutical active ingredients originates from developed countries like the USA, the European Union (EU) countries and Japan and 20% comes from developing countries.
Increasing demand	The attitude of pharmaceutical industries towards medicinal plants and natural products has changed dramatically over the past two decades.
Awareness	Increased awareness and interest in medicinal plants both general public and scientific community.
Pharmaceutical companies	In 1980 a few of the top 250 pharmaceutical companies had research activities involving higher plants, but by the early 1990s more than half of them had introduced such programmes.
Global import	1966 to 1991. Plant alkaloids and derivatives has increased from 1.9 to 11.4 million metric tonnes. Glycosides and their derivatives from 0.3 to 2.9 million metric tonnes. Terpenoids contributes from US$ 12.4 billion in 2002, at an AAGR of 10.1 per cent. Flavonoids, saponins, anthraquinones and digitalis compounds are among the most important groups within this category.
Examples	Belladona, cinchona, poppy, rauwolfia, vinca and others.

Table 8.2: Trends in global nutraceuticals market

Heading	Details
Growth potential	Nutraceuticals industry is a promising sector with enormous growth potential.
Major producer and consumer	The USA leads the market followed by Western European countries and Japan as both major producer and consumer of nutrceuticals.
Annual growth rate (1998-99)	The herbal supplements and vitamins were the strongest performing sector in the global OTC market, with an annual growth rate 27 of 16 per cent.

World Market for Herbal Medicines

The herbal medicine industry is one of the fastest growing industries in the world. Global market for herbal medicines was estimated at US$ 12.4 billion in 1994, increasing to US$ 19.6 billion in 1999.

Natural health products herbs have been used for thousands of years by indigenous people for medicinal and healing purposes. In recent years, with the expansion of consumer's interest in the health benefits of foods and personal care products, more attention is being paid to the health foods (nutraceuticals), cosmetics and personal care products (cosmeceuticals) containing natural ingredients. The major factors for their growing demand are aging population of industrialized countries, growing desire for alternatives to conventional pharmaceutical products, and increased awareness of consumers for health benefits of these products.

Nutraceutical is the latest term for health foods, first coined in 1996 by Stephen DeFelice, founder of the foundation for innovation in medicine of New Jersey, USA. The term 'nutraceuticals' is an amalgamation of the terms 'nutrition' and 'pharmaceuticals' used as a marking level to distinguish certain foods and food ingredients, usually from natural sources, which confer specific health benefits.

Worldwide Demand of Nutraceuticals

The global nutraceuticals product market holds a considerable possibility for growth

and projected to increase significantly within the next six years. Nutraceuticals are multipurpose in nature as they are used in numerous industries such as pharmaceutical food and beverages, animal feed additives, and personal care. Nutraceutical products are the requirement of the modern world. The market is self-assured to see noteworthy development and increase in demand for nutraceuticals-containing products.

The nutraceutical industry lies under four main segments which include:

- Functional foods
- Dietary supplements
- Herbal/natural products
- Personal care

The worldwide demand of nutraceutical market is estimated as USD 117 billion (INR 5148 billion). In India, "nutraceuticals" is still beginning stage. But its demand is increasing worldwide by CAGR of 18% for the last few years. The most quickly emerging segments are dietary supplements (approx. 19.5 percent per year) and natural/herbal products (approx. 11.6 percent per year). Global nutraceuticals market size is expected to reach $302,306 million by 2022 from $184,092 million in 2015 with a CAGR of 7.04% from 2016 to 2022.

Antioxidants and herbal teas also form an important part of the nutraceuticals market. The leading antioxidant phytochemicals in demand are vitamins A, C, and E, carotenoids and flavonoids.

Phytocosmetics and Personal Care Products

Cosmetic manufacturers began to use the term cosmeceuticals to describe OTC skin care products such as alphahydroxy acids and vitamins. Thus, cosmeceuticals are well defined as the products, which lie on the boundary line between drugs and cosmetics which possess desirable physiological activities, such as skin healing, antioxidant, and smoothing or conditioning properties.

Cosmeceutical Industry

The cosmeceutical market has erupted with the addition of new active ingredients, the discovery of enhanced technologies, and the spreading of cosmeceutical ingredients to the make up and hair-care products. Manufacturers are frequently replacing vitamins with herbal ingredients, such as saw palmetto, ginseng and ginkgo.

Worldwide Demand of Cosmeceuticals

Global cosmeceuticals market offers huge potential in the Asian countries, such as Japan, China, and India, which are also set to attract major players in future. Japan has already made a niche mark in the global cosmetics market and its position in the cosmeceuticals (having quasi-drug status) segment is effectively improving. Among the global cosmeceuticals industry, skin care is the most important segment and is expected to grow significantly in the years to come as increasing number of people entering the middle age of life will create more demand for cosmeceuticals product. The global cosmeceuticals market is forecasted to reach USD 85 billion by 2024 growing at a CAGR of 8.81% during the forecast period (2019–2024). Countries, such as the United States, Canada, United Kingdom, Germany, and other European countries held a prominent share in the global cosmeceuticals market. China, India, and Vietnam present considerable growth opportunities for the market players, primarily due to the growing millennial population. Furthermore, raising awareness regarding cosmeceuticals and cosmetics products, such as anti-aging, sun care, and hair care products, is expected to drive the growth potential in the near future.

EXPORT AND IMPORT OF HERBAL FORMULATION

Major Importing Regions and Countries

The EU, the USA and Japan are the biggest consumer markets of medicinal plant materials. Europe, Germany, France, Italy, and

Spain are the major markets for medicinal herbs. Germany dominates the European trade in medicinal plants as it dominates the European market for phytopharmaceuticals. The major importers of medicinal plants in Asia are Hong Kong, Japan, Singapore and Malaysia. The volumes of material used in the traditional systems of medicine, particularly in Asia, are of great concern while considering the demand for medicinal plants. China also imports significant volumes of medicinal herbs apart from being largest producer and exporter of medicinal herbs.

Major Exporting Regions and Countries

China and India were the leading exporting countries of medicinal plant material to the world market with average annual export volumes of 140,000 metric tonnes and about 35,000 metric tonnes respectively. Other major exporting countries among the top twelve are: Germany, Singapore, Egypt, Chile, the USA, Morocco, Mexico, Pakistan, France and Thailand. The significant volumes of medicinal plants also originate from Albania, Brazil, Bulgaria, Hungary, Korea, Turkey, and smaller market share runs from Kenya, Mauritius and Indonesia. Singapore and Hong Kong are the main re-exporters of medicinal plants to the world market.

Production and Exports of Traditional Medicines

China and India are the two largest producers of medicinal plants and account for 40% of global biodiversity. However, China has established itself as the major exporter of traditional herbal medicines in the world market, with exports to the tune of US$ 5 billion per year, as against US$ around 240 million by India. India needs to organize itself well to achieve a significant share in this growing market segment. Almost 90% of the collection of medicinal plants is from the wild. Since 70% of plant collections involve destructive harvesting, many plants are endangered or vulnerable and threatened. China and India are major sources of medicinal plants. Whereas China's sales of herbal products is in the range of ₹ 25000 crore, India holds only 1% of the global market, selling roughly ₹ 500 crore worth of products. In the European Union, sales of herbal products raised from US 1.6 billion to 3.3 billion in 1998. The market is huge and it is growing. The global market for herbal products is exploding. It is estimated to touch 5 trillions by 2020.

Market Value of Herbal Medicine

India's share in the export of herbals is USD 63 billion which is just 0.2% of the global herbal market. So there is obviously vast scope for Indian manufacturers for entering the growing worldwide opportunity of business in herbal pharmaceutical field. In many countries our product can be registered and thus can gain the necessary reliability for their export. The registration guidelines for every country are different and unique, hence a thought should also be given to the possibility of melting such requirements before identification of market for our product. Global awareness for quality is high and we must emphasize on quality building into the product. The manufacturing facilities and infrastructure should comply with the GMP standards. Our own drugs and cosmetics law and rules define GMP for traditional medicinal products, in schedule T and every effort should be made by each and every manufacturer so as to comply with these standards.

Global Demand on Herbal Drugs

The global herbal medicine market is expected to register a CAGR of 5.88% to reach USD 1,29,689.3 million by 2023. The global herbal medicine market, by form, is segmented into extracts, powders, capsules and tablets, syrups, and others. The extracts segment accounted for the largest market share of 36.95% in 2017. The prominent players in the global herbal medicine market are Arkopharma, Bayer AG, Beovita, Hishimo Pharmaceuticals, Schaper and Brümmer,

ZeinPharma Germany GmbH, Venus Pharma GmbH, Dasherb Corp, and Arizona Natural Products among other. In India the medicinal plant market is unorganized at present. Pharmaceutical industries are responsible for inefficient, imperfect, informal and opportunistic marketing of medicinal plants. Herbal drug trade is vast, secretive and unregulated.

CONCLUSION

Medicinal herbs as potential source of therapeutics aids have attained a significant role in health system all over the world for both humans and animals not only in the diseased condition but also as potential material for maintaining proper health. Undoubtedly, the demand for plant-derived products has increased across the world. Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating diseases. Nature is always a golden sign to show the prominent phenomena of coexistence. Natural products from plants, animals and minerals are the basis for treating human diseases. Medicinal plants are presently in demand and their acceptance is increasing progressively. Undoubtedly, plants play an important role by providing essential services in ecosystems. Without plants, humans and other living organisms cannot live in a way living should be. Anyway, herbals especially medicinal herbs have constantly acted as an overall indicator of ecosystem health.

Medicinal plants are used for treatment because they have definite properties, including synergistic actions. The constituents of the plant may interact with each other, and this interaction can be beneficial for both or adverse to either of them or eliminate the harmful effects of both. Plant-derived compounds can dramatically improve hard-to-treat illnesses, such as cancer. Plant components are also characterized by their ability to prevent the development of certain diseases. The toxicity and adverse effects of conventional and allopathic medicines have also been important factors in the sudden increase in population demands and increase in the number of herbal drug manufactures as well as a reduction in the use of chemical drugs.

CHAPTER 9

Herbal Drugs Commonly Used for Formulation Developments

Plant metabolites are chemical compounds that are necessary for their basic functions, i.e. biochemical pathways for survival and propagation. Basic or primary metabolism refers to all biochemical processes for the normal anabolic and catabolic pathways which result in assimilation, respiration, transport, and differentiation, while secondary metabolisms generate diverse and seemingly less essential or non-essential byproducts. These secondary products give the colors, flavors, and smells to the plant. Plant metabolites of medicinal importance form an extensively diverse group of chemical compounds showing greater variation in solubility and stability. They can be broadly classified as follows:

1. Fixed oils, fats and waxes (lipids)
2. Phenols
3. Tannins
4. Proteins
5. Alkaloids
6. Carbohydrates
7. Glycosides
8. Volatile oils, and
9. Resins and resin combinations

Primary metabolites consist of many different types of organic compounds, including carbohydrates, lipids, proteins, and nucleic acids. They are available universally in the plant kingdom as they are the components or products of fundamental metabolic pathways or cycles such as glycolysis, the Krebs cycle, and the Calvin cycle. They are responsible for normal growth and reproduction of plants. Examples include energy-rich fuel molecules, such as sucrose and starch, structural components such as cellulose, informational molecules such as DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), and pigments, such as chlorophyll.

In addition to having fundamental roles in plant growth and development, some of the primary metabolites are precursors (starting materials) for the synthesis of secondary metabolites.

Secondary metabolites mainly consist of three classes of compounds: Alkaloids, terpenoids, and phenolic. However, these classes of compounds also include primary metabolites, so whether a compound is a primary or secondary metabolite is a distinction based not only on its chemical structure but also on its function and distribution within the plant kingdom. Many thousands of secondary metabolites have been isolated from plants, and many of them have powerful physiological effects in humans and are used as medicines. They are major component of plant defense mechanism against herbivores, pest and pathogens. They also attract pollinators and seed dispersing materials. It produces product that aid in growth and development of plant but not required for plant to survive.

CARBOHYDRATES

Carbohydrates are the most abundant class of organic compounds found in living organisms containing the elements carbon, hydrogen, and oxygen. They are either aldehydic or ketonic alcohols in which hydrogen and oxygen are present in the same ratio as in water. Carbohydrates are widely used in

pharmaceutical preparations in numerous applications.

They originate as products of photosynthesis, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll. They are hydrates of carbon $C_nH_2O_n$. Chemically made up of skeletal C, H which is usually 2× the number of C, highly variable number of O, occasional N and S. Carbohydrates are defined as polyhydroxyaldehyde or polyhydroxyketone, or substance that gives these compounds on hydrolysis.

They are broadly classified into three major groups:

1. True sugars
   a. monosaccharides
   b. oligosaccharides
2. Polysaccharides and
3. Derived carbohydrates

True sugars

a. Monosaccharides.
   i. Pentoses: L-arabinose, D-xylose, D-ribose, and apiose.
   ii. Hexoses: D-glucose (dextrose), D-fructose (levulose), D-mannose, and L-galactose.
b. Oligosaccharides (less than 9 monosaccaride units). Those occurring naturally are usually di-, tri-, and tetrasaccharides.
   i. Disaccharides: Non-reducing: Sucrose, trihalose.
   Reducing: Maltose, lactose, turanose, cellobiose, gentiobiose, melibiose.
   ii. Trisaccharides: Raffinose (non-reducing).
   iii. Tetrasaccharides: Stachiose (non-reducing).

Polysaccharides (non-sugars)

a. Starch: It is the principal food reserve of plants. It gives alpha-D glucose on complete hydrolysis, it is formed of amylose, which is a straight chain of alpha-1,4-glycosidic bonds (more soluble in water) and amylopectin, which is branched presumably through an additional alpha-1,6-glycosidic bond (less soluble in water and more viscous in solution).
b. Dextrins: Obtained by incomplete hydrolysis of starch.
c. Glycogen, which is the reserve polysaccharide of the animal kingdom.
d. Inulin, a fructosan (molecular weight about 5000) consisting of a linear chain of B-(1, 2)-fructofuranose units.
e. Cellulose, the most widely distributed skeletal polysaccharide and most.

Chemical Test of Carbohydrates

1. Test for starch: To the solution of carbohydrates add 2–3 drops of iodine, blue/black precipitate (ppt) forms.
2. Test of reducing sugar: To the solution of carbohydrates add equal quantity of Benedict's reagent mix. Heat to 70°C (Do not boil because this would split a disaccharide, e.g. sucrose into reducing sugars (glucose and fructose) and give a false positive test). Solution turns from blue to pale green to yellow to orange to brick red ppt of copper (I) oxide, e.g. glucose, fructose and maltose.
3. Test of non-reducing sugar: To 2 cm 3 test solution add 1 cm 3 dilute HCl. Boil. Cool and neutralize with excess NaOH. Repeat test for reducing sugar.

Functions of Carbohydrates

1. Immediate respiratory substrates, e.g. glucose
2. Energy stores, e.g. glycogen in mammals, starch in plants
3. Structural components, e.g. cellulose in plant cell walls, chitin in arthropod exoskeleton
4. Pentose sugars—ribose and deoxyribose are components of RNA and DNA respectively.
5. Metabolites, i.e. intermediates in biochemical pathways
6. Cell-to-cell attachment molecules, e.g. combined with proteins to form glycoproteins or lipids to form glycolipids on plasma membrane.

HONEY

Synonyms: Madhu, Mel, purified honey.

Biological source: Honey is obtained from the sugary secretion deposited in honeycomb by bees *Apis mellifera* and *Apis dorsata*, Family Apidae.

Habitat: West Indies, California, Chile, Africa, Australia, New Zealand.

Organoleptic characters (Fig. 9.1)

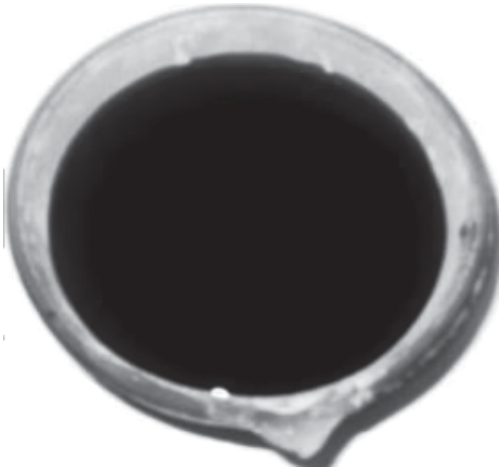


Fig. 9.1: Honey

Color: Yellowish-brown liquid

Odor: Characteristic, pleasant

Taste: Sweet

Appearance: Syrupy thick, clear, viscid and translucent liquid when fresh.

Weight per ml: 1.35 to 1.36

Solubility: Soluble in water, insoluble in alcohol and other organic solvents.

Rotation: Optically active with rotation between +0.6 and 0.3.

Chemical constituents: Honey mainly consists of natural invert sugar, which is a mixture of glucose (30–40%) and fructose (40–50%). It also contains sucrose, dextrin, formic acid, volatile oil and pollen grains in small amount together with vitamins, proteins and amino acids and traces of invertase and diastase enzymes (Fig. 9.2).

Table 9.1: Composition of honey

S. No.	Constituents	Percentage
1.	Water	17–18%
2.	Levulose (fructose)	39%
3.	Dextrose (glucose)	34%
4.	Sucrose	1%
5.	Dextrin	0.5%
6.	Plant acids	0.5%
7.	Proteins	2%
8.	Salts	1%
9.	Undetermined residues	4%

Chemical test: Honey solution is prepared by mixing one part of honey with five parts of water.

- Reduction of Fehling's solution: 1 ml of honey solution with 1 ml of Fehling's solution on heating red color is produced due to reduction.
- Test for artificial invert sugar: 5 ml of honey solution + 2.5 ml of diethyl ether, shake and separate the ether layer, evaporate ether layer completely and to the residue add one drop of 1% w/v solution of resorcinol in concentrated HCl pure honey should not give cherry red color. (*Note:* Due to prolonged heating long storage sometime pure

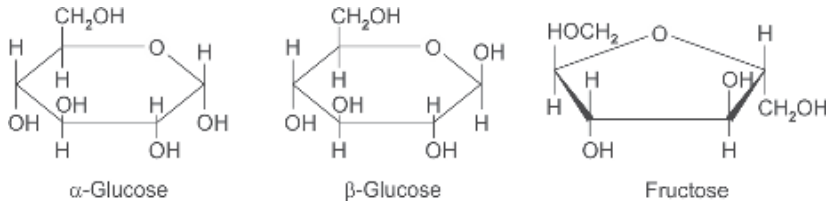


Fig. 9.2: Chemical constituents of honey

honey also give cherry red color), honey adulterated with artificial invert sugar due to presence of furfural give cherry red color.
- Limit test: Limit test for chloride and sulphate are important as per pharmacopoeial standard.

Adulterants: Artificial invert sugar, commercial glucose, sucrose and polysaccharides.

Uses: It is used as a nutritive, as a demulcents in cough, cold and constipation, also as a laxative, antiseptic and vehicle for ayurvedic preparations.

AGAR

Synonyms: Agar-agar, vegetable gelatin, Japanese or Chinese gelatin, Japanese isinglass.

Biological source: It is the dried colloidal concentrate prepared from the decoction of red algae and from other species of the genus *Gelidium*, family Gelidaceae. The genus *Gelidium* provides about 35% of the total raw material. Japanese agar is obtained from *Gelidium amansii*. It is also obtained from genus *Gracilaria*, family Gracilariaceae.

Habitat: Agar is produced on large scale in Japan, Korea, South Africa, USA, Spain, Mexico and New Zealand.

Botany:
- *Kingdom:* Archaeplastida
- *Division:* Rhodophyta
- *Class:* Rhodophyceae
- *Subclass:* Rhodymeniophycidae
- *Order:* Gelidiales
- *Family:* Gelidiaceae
- *Genus: Gelidium*

Morphological characters (Fig. 9.3)
Form: Occurs in two forms: 1. Coarse powder or flakes 2. bundles of translucent, and crumpled, strips, 2–5 mm wide.

Color: Colorless to pale yellow.

Fracture: Tough when damp and brittle when dry.

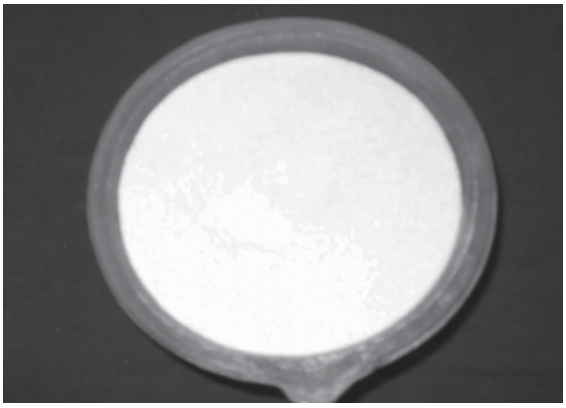


Fig. 9.3: Agar

Odor: Not distinct

Taste: Mucilaginous

Solubility:
- *Cold water:* Does not dissolve but swells to a gelatinous mass,
- *Boiling water:* Dissolves and 1% solution gives a stiff jelly on cooling

Chemical constituents: Agar is a heteropolysaccharide which contains a calcium salt of sulphuric ester of carbohydrate complex. It consists of two principle constituents, agarose and agaropectin.
- Agarose is the neutral polymer of galactose disaccharides known as agarbiose and responsible for gel strength
- Ageropectin is responsible for the viscosity of agar solution, is a sulphonated polysaccharides of galactose and uronic acid esterified with sulphuric acid (Fig. 9.4).

Chemical test:
- Agar with iodine solution gives crimson to brown color

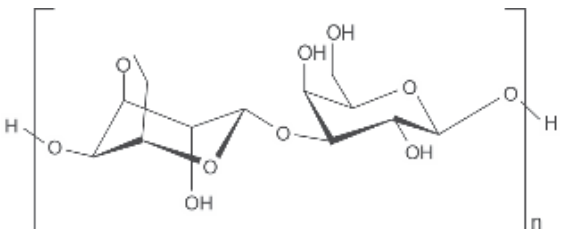


Fig. 9.4: Agarose

- Agar solution with ruthenium red gives pink color
- Agar solution (hot) with $BaCl_2$ gives white precipitate.
- Agar with Fehling's solution (heat) gives red precipitate.
- Boil agar solution with water forms stiff jelly on cooling.
- Agar ash on slide with 2 drops of HCl when observed under microscope sponge spicules of diatoms are seen.

Uses: Agar is widely used as a treatment for constipation, but is usually employed with Cascara. It does not increase peristaltic action. Its therapeutic value depends on the ability of the dry agar to absorb and retain moisture. Its action is mechanical and analogous to that of the cellulose of vegetable foods, aiding the regularity of the bowel movements. It is sometimes used as an adulterant of jams and jellies. It is mainly used for preparation of nutrient media in bacteriological preparations.

Adulterants: The powdered drug is adulterated with starch. Mount the drug in chloral–iodine solution and observe the starch grains.

ACACIA

Synonyms: Gum acacia, gum arabic.

Biological source: Acacia gum is a dried exudation from the stem and branches of *Acacia senegal*, family leguminosae.

Habitat: Sudan, central and western African countries such as Senegal, Nigeria and Senegambia.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Fabales
- Family: Fabaceae

Subfamily: Mimosoideae

- Genus: *Acacia*
- Species: *Senegal*

Fig. 9.5: Acacia gum

Parts used: Gummy exudates from stems and branches.

Collection and preparations: The gum harvest from the various species lasts about five weeks. About the middle of November, after the rainy season, it exudes spontaneously from the trunk and principal branches, but the flow is generally stimulated by incisions in the bark, a thin strip, 2 to 3 feet in length and 1 to 3 inches wide being torn off. In about fifteen days it thickens in the furrow down which it runs, hardening on exposure to the air, usually in the form of round or oval tears, but sometimes in vermicular forms, white or red, according to whether the species is a white or red gum tree. About the middle of December, the Moors commence the harvesting. The masses of gum are collected, either while adhering to the bark, or after it falls to the ground, the entire product, often of various species, thus collected, is packed in baskets and very large sacks of tanned leather.

Characteristics:

- Gum Arabic is unique among the natural hydrocolloids because of its extremely high solubility in water. Gum arabic is insoluble in oils and in most organic solvents. It is soluble an aqueous ethanol up to a limit of about 60% ethanol. Limited solubility can also be obtained with glycerol and ethylene glycol.

- It can actually form a highly viscous, gel-like mass similar in character to a strong starch gel.
- High viscosities are not obtained with gum arabic until concentrations of about 40–50% are obtained. This ability to form highly concentrated solutions is responsible for the excellent stabilizing and emulsifying properties of gum arabic when incorporated with large amounts of insoluble matters.

Chemical constituents: Acacia gum consists almost entirely of a glucosidal acid of high molecular weight, which has been termed arabic acid, combined with potassium, magnesium, and calcium; by hydrolysis each molecule yields two molecules of the sugar arabinose and four of galactose. Gum acacia also contains an oxydase enzyme, and hence readily turns powdered guaiacum resin. It contains further a small percentage of nitrogen (Fig. 9.6).

Chemical test:

- Acacia gum is insoluble in alcohol, but dissolves freely in water, forming a translucent, viscid, but not glairy or ropy liquid, that feebly reddens litmus paper.
- A 10% aqueous solution of good qualities is slightly laevorotatory, and when boiled with an equal volume of Fehling's solution throws down a slight but distinct deposit of cuprous oxide.
- Solution of lead acetate produces no precipitate, but subacetate produces a copious white.
- A saturated solution of borax forms with a strong solution of gum a clear, translucent jelly.
- Inferior (brown) gum usually contains tannin which may be detected by solution of ferric chloride.

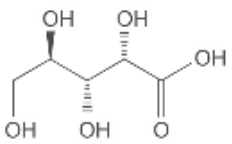


Fig. 9.6: Arabic acid

Uses: Acacia gum is used medicinally as a demulcent and as a means of suspending oils, resin, etc, in aqueous fluids.

TRAGACANTH

Synonyms: Gum tragacanth, Syrian tragacanth, gum dragon.

Biological source: Tragacanth is the gummy exudation obtained from the gummy exudation of *Astragalus gummifer*, family Leguminosae.

Habitat: Asia minor, persia and kurdistan.

Botany:

- *Kingdom:* Plantae
- *Division:* Magnoliophyta
- *Class:* Magnoliopsida
- *Order:* Fabales
- *Family:* Fabaceae
- *Genus:* Astragalus
- *Species:* Gummifer

Parts used: Gummy exudation.

Description: The plant is a small branching thorny shrub, the stem of which exudes a gum, vertical slits giving flat ribbon-shaped pieces and punctures giving tears; these have a horny appearance, are nearly colorless or faintly yellow, marked with numerous concentric ridges, the flakes break with a short fracture, are odorless and nearly tasteless; soaked in cold water, they swell and form a gelatinous mass 8 or 10 per cent only dissolving (Fig. 9.7).

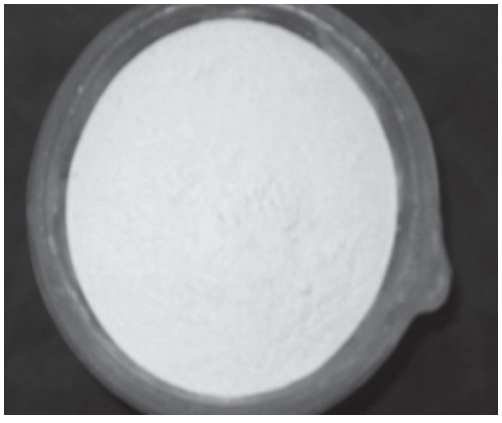


Fig. 9.7: Tragacanth gum

Chemical constituents: The portion soluble in water contains chiefly polyarabinan-trigalaetangeddic acid (tragacanthin consisting of tragacanthic acid and an arabinogalactan) and the insoluble part is called bassorin. As well as 1–3% starch, 1–4% cellulose; 3% ash, small amounts of invert sugar, 2–3% of a volatile acid (probably acetic acid), and about 15% water. Tragacanthic acid is composed of 40% D-galacturonic acid, 40% D-xylose, 10% L-fucose, 4% D-galactose, and three aldobiuronic acids. Arabinogalactan consists of 75% L-arabinose, 12% D-galactose, 3% D-galacturonic acid, and small amounts of L-rhamnose. Bassorin is reported to contain about 5% methoxyl groups.

Characteristics:

- *Color:* White or pale yellowish white flakes
- *Odor:* Odorless
- *Taste:* Tasteless
- *Size:* Flakes are 25 × 12 × 2 mm
- *Shape:* Thin flattened ribbon like
- *Solubility:* Partly soluble in water, swells, insoluble in alcohol
- *Fracture:* Short

Extra features: The gum is horny, translucent, transverse and longitudinal ridges.

Chemical test:

- Tragacanth gum is boiled with 10% aqueous ferric chloride solution deep yellow precipitate is obtained.
- Tragacanth gum if dissolved in precipitated copper oxide and conc. ammonium hydroxide stingy precipitate is obtained.
- Gum in lead acetate gives white precipitate.
- Gum in Fehling's solution gives red precipitate.
- Gum in 5% caustic potash gives canary yellow color.

Uses: Demulcent, but owing to its incomplete solubility is not often used internally. It is much used for the suspension of heavy, insoluble powders to impart consistence to lozenges, being superior to gum arabic, also in making emulsions, mucilago, etc. Mucilage of Tragacanth has been used as an application to burns; it is also employed by manufacturers for stiffening calico, crape, etc.

Adulterants: The Indian gum, the product of *Coplospermum gossypium*, also acacia, dextrin wheat and corn starch.

ISAPGOL

Synonyms: Bengali: Isapgul, Hindi: Isapgol, English: Indian psyllium.

Biological source: Dried seeds of *Plantago ovata* forsk, family plantaginaceae.

Habitat: Mediterranean region and commercially grown in north western India.

Botany:

- *Kingdom:* Plantae
- *Division:* Magnoliophyta
- *Class:* Magnolipisida
- *Order:* Lamiales
- *Family:* Plantaginaceae
- *Genus:* Plantago
- *Species:* Ovate

Parts used: Seeds, Husk.

Organoleptic characters (Fig. 9.8)

- *Color:* Light brown to moderate brown
- *Odor:* Faint
- *Taste:* Bland, mucilaginous

Extra features: Seeds have convex and concave surface, convex surface has central glossy reddish brown elongated spots,

Fig. 9.8: Isapgol seeds

whereas concave surface is deeply groved with hilum.

Chemical constituents: Seed contain 30% mucilage, xylose, arabinose, galaecturonic acid, rhamnose, galactose, albumin, tannin and acetylcholine. The seed pulp contains 14.7% lilonic acid and 5% stable oil.

Chemical test: Test for mucilage.

- Seeds on slide with water show the zone of mucilage.
- Isapgol powder when treated with water forms jelly-like mass on keeping.
- Mucilage gives pink color with ruthenium red under microscope.

Standards:

- *Total ash:* Not more than 4.0%
- *Particle size:* Not more than 5.0%
- *Moisture (loss on drying):* Not more than 12.0%
- *Acid insoluble ash:* Not more than 1.0%
- *Foreign organic matter:* Not more than 0.5%

Microscopy: Ovoid-oblong, boat shaped 2–3 mm long, 0.8–1.5 mm wide, endospermic, pinkish grey to brown in color. The dorsal surface is convex with a small, elliptical or elongated shining reddish brown spot while the ventral surface is concave with a deep furrow, odor characteristics, and taste mucilaginous. Epidermal cell of testa is filled with mucilage which swells in contact with water. The cells are large. Polyhedral, thin walled, rounded in surface view. Small starch granules are simple or compound embedded in the mucilage. Inner layer of testa rather indistinct, thin walled, cells containing brown pigment. Endosperm is composed of thick walled cells with numerous piths and granular contents, embryo consisting of thin-walled polyhedral cells containing fixed oil and aleuronic grains.

Uses: The characteristics of psyllium seed husks make them useful for any treatment that requires improvement or maintenance of transit time in the gastrointestinal tract, since the inert bulk of the husks helps provide a constant volume of solid material irrespective of other aspects of the diet or any disease condition of the gut. Psyllium seed is considering as a good intestinal cleanser and stool softner. Psyllium seed is one of the most popular fibers used. The seeds are primarily used in traditional herbal medicine. Psyllium seed husks are mainly used to treat constipation.

Adulterants: *Plantago lanceolata.*

STARCH

Synonyms: Amylum

Biological source: Starch or amylum is a polysaccharide carbohydrate produced by all green plants as an energy store and is a major food source for humans. Potato, rice, maize and wheat starch is obtained from *Solanum tuberosum* (Solanaceae), *Oryza sativa* (Gramineae), *Zea mays* (Gramineae), *Triticum astivum* (Gramineae), respectively.

Habitat: Commercially starch is produced in USA, India, China and Japan.

Organoleptic characters (Fig. 9.9)

- *Color:* Rice and maize—white, potato—slightly yellowish, wheat—cream
- Odor: Odorless
- Taste: Mucilaginous
- Solubility: Insoluble in alcohol and cold water, but form colloidal solution with boiled water.

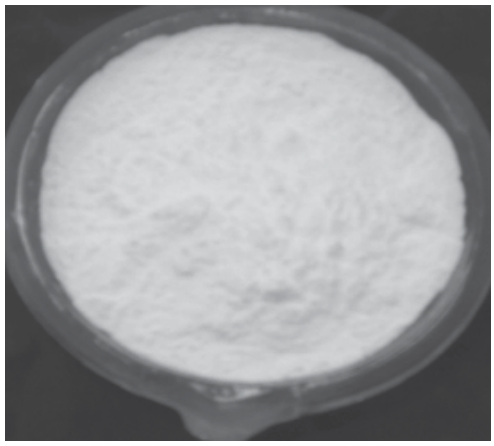


Fig. 9.9: Starch

- Specific gravity: 1.62–1.65
- pH: Potato and maize—neutral, rice—alkaline, wheat—faint acidic.

Extra features: A typical feature of starch is that it becomes soluble in water when heated. The granules swell and burst, the semi-crystalline structure is lost and the smaller amylose molecules start leaching out of the granule. This process is called starch gelatinization.

Microscopical Characteristic

Potato starch: Potato starch is mostly simple or compound. Subspherical grains are up to 35 μ in length and ovoid grains of 30 to 100 μ. They have usually a flattened ovoid shape and possess a small hilum that is often situated near the narrow extremity of the grain, whilst the broad end frequently exhibits a sinuate outline; the concentric striae are well marked.

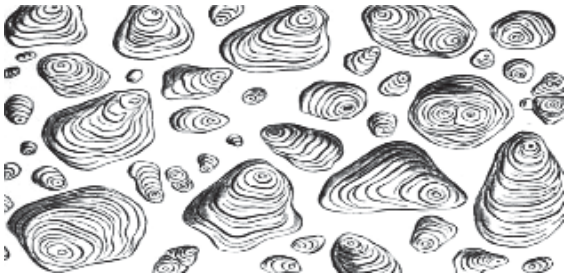


Fig. 9.10: Potato starch

Rice starch: The rice starch is simple and compound with polyhedral shape. No striations are visible but hilum can be distinguished by small central dot. The grains are up to 4 to 10 μ.

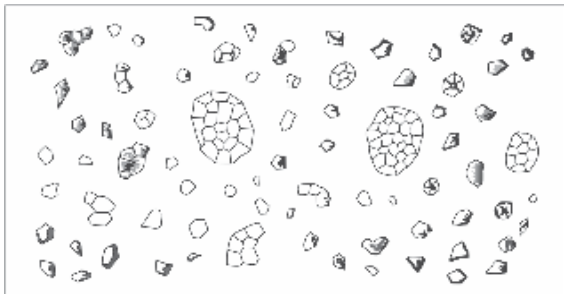


Fig. 9.11: Rice starch

Maize starch: Maize starch consists of grains that are nearly uniform in size and rather smaller than the large grains of wheat starch; (mostly 12 μ to 18 μ; they are polygonal with blunt angles, or more or less rounded). In the centre there is often a small cleft, or two or three radiating from a centre (the hilum).

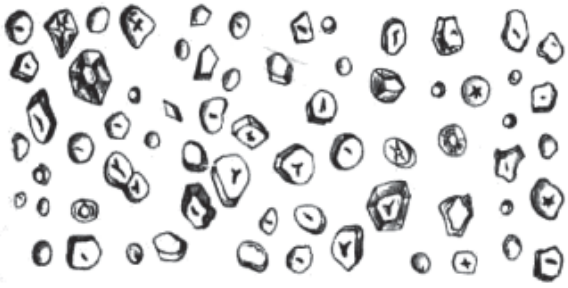


Fig. 9.12: Maize starch

Wheat starch: Wheat starch consists of large and small grains mixed together, with few intermediate in size; the former are lenticular in shape and sometimes marked with faint concentric rings. The hilum is central but not conspicuous. The larger of the large grains average about 30 to 38 microns 1 (μ) in diameter, the smaller of the large grains 15 to 25, whilst the small grains average 6 to 7.

Fig. 9.13: Wheat starch

Preparation of starch: The cells are ruptured by grinding the softened grain to a pulp, and the gluten is removed by one of the following processes, viz.:

a. A mixture of crushed grain and water is allowed to undergo putrefactive decomposition; the gluten is decomposed, lactic, acetic, and other acids being produced and removed by washing.

b. The crushed grain is mixed with a dilute solution of caustic soda by which the gluten is dissolved.
c. The grain is crushed and mixed with water to dough from which the starch grains are washed by kneading it in a stream of water, leaving a mass of gluten behind.

The starch is purified by washing, straining and allowing the milky liquid containing starch grains in suspension to clear, by which a more or less complete separation into pure starch and starch mixed with varying amounts of cell-debris is effected. It is finally dried, during which the moist mass gradually splits up into angular fragments. These are then ground to form starch powder.

Chemical constituents: Starch consists of two types of molecules, amylose (normally 20–30%) and amylopectin (normally 70–80%). Both consist of polymers of α-D-glucose units. Amylose and amylopectin are inherently incompatible molecules; amylose having lower molecular weight with a relatively extended shape, whereas amylopectin has huge but compact molecules. The presence of amylose tends to reduce the crystallinity of the amylopectin and influence the ease of water penetration into the granules. As they absorb water, they swell, lose crystallinity. The higher the amylose content, the lower is the swelling power and the smaller is the gel strength for the same starch.

Chemical test: Starch is a polysaccharose of the formula $(C_6H_{10}O_5)n$. Boiled with water the grains swell, burst and partially dissolve, forming an opalescent solution which, sufficiently concentrated, gelatinises on cooling (starch paste).

Starch test: Add iodine-KI reagent to a solution. A blue-black color results if starch is present. If starch amylose is not present, then the color will stay orange or yellow. Starch amylopectin does not give the color, nor does cellulose, nor do disaccharides such as sucrose in sugar.

It shows positive Fehling's and Molish test.

Uses: Starch is a versatile and cheap, and has many uses as thickener, water binder, emulsion stabilizer and gelling agent. Internally it is used as astringent, nutritive, demulcent, protective and absorbent. It is used as antidote in iodine poisoning. It is used as filler, binder and disintegrator in tablet. Starch is starting material for preparation of glucose, dextrose and dextrin.

GLYCOSIDES

Glycosides are non-reducing substances that, on hydrolysis brought about by reagents or enzymes, yield one or more reducing sugars among the products of hydrolysis. The non-sugar part of the molecule is called the aglycone or genin; the sugar component is called the glycone.

Glycosides are the natural organic compounds, from plants or animal sources which on enzymatic or acid hydrolysis give one or more sugar moieties along with non-sugar moieties. These two different chemical compounds or compounds are present in joined form in glycosides by a special linkage called glycosidal linkage. In which the former is called glycone and the later aglycone or genin. Glycone is the sugar moiety and aglycone is the non-sugar moiety. In other words, glycosides are the naturally occurring plant constituents which consists of a sugar portion attached by a special glycoside linkage to non-sugar portion.

Chemical aspects: Chemically the glycosides are considered as acetals in which the hydroxyl group of the sugar is condensed with a hydroxyl group of the non-sugar component and the secondary hydroxyl is condensed with in the sugar molecule itself to form an oxide ring so glycosides are also called sugar ether.

The usual linkage between sugar and aglycone is oxygen linkage which is between the reducing group of sugar and an alcoholic or phenolic group of aglycone and such glycosides are called O-glycosides. As sugar is found in two forms so, glycosides are of two

types: α and β. α glycosidic bond gives α glycosides while β glycosidic bond gives β glycosides.

Glycosides can be hydrolyzed by enzyme, acid, alkali or sometimes only with moisture. The enzymes hydrolysed α-glycosides are invertase and maltase while myrosin, linarase, amygdalase, cellobiase and gentianase hydrolysed β-glycosides. Stereochemically, α and β stereoisomers are assigned. In simple form, the glycosides with these two isomers can be synthesized from union of methyl alcohol and glucose.

Aglycones

The aglycones or genin is that part of a glycoside molecule which is responsible for the pharmacological action of the drug of the glycosides. The aglycones belong to variety of different classes of definite chemical belong to compounds, thus the glycosides can be grouped as cyanogenetic glycosides (amygdalin), glycosinolates (glucocapparin), lactone or coumarin (dasphnin, digitoxin), quinine glycosides (barbaloin), flavanoid (quercetin), steroidal alkaloid (salanine), saponin (glycyrrhizin).

Sugar

Mainly all kinds of sugars are present in the glycosides. They may be tetrose, pentose, hexoses or some special sugar, as in cardiac glycosides. When sugar moiety is glucose, fructose, rhamnoside, galactoside and riboside then glycosides are glycoside, fructoside, rhamnoside, galactoside and riboside respectively.

The glycosidic linkages: The usual linkage between the sugar and aglycone is an oxygen linkage, connecting the reducing group of a sugar and an alcoholic or phenolic hydroxy group of the aglycone.

O-glycosides are the most common ones found in nature.

S-glycosides and N-glycosides: In S-glycosides (e.g. sinigrin), the sugar is linked to the thiol (sulfhydryl) group of the aglycone. In N-glycosides (e.g. the streptidine moiety of streptomycin, glucosamine, or adenosine), the sugar is linked to the amino group of the aglycone.

C-glycosides (e.g. barbaloin) in which the sugar is linked to the aglycone by a carbon-to-carbon bond.

Properties: Glycosides are colorless, crystalline or amorphous solid substances. Flavones glycosides are yellow colored and anthracene glycosides are red or orange colored. They are soluble in water and alcohol but insoluble in ether and chloroform. Glycosides are optically active and usually they are laevorotatory means l-form. Glycosides are substances of profound physiological action or animal tissue and are many a times poisonous for human beings. They are generally the products of special metabolic process and their concentration in various morphological parts also varies considerably according to age and ecological factors of the plant. Those which are most significant therapeutic action are cardiac glycosides.

Classification

Glycosides are usually classified into the following groups using the chemical nature of the aglycone.

1. Phenol (e.g. arbutin)
2. Alcohol (e.g. salicin)
3. Lactone or coumarin (e.g. daphnin)
4. Flavone (e.g. rutin)
5. Anthraquinone (e.g. gluco aloe-emodin)
6. Aldehydes (e.g. glucovanillin)
7. Cyanophore (e.g. amygdalin)
8. Thiocyanate (e.g. sinigrin)
9. Steroid (e.g. digitoxin)
10. Saponin (e.g. digitonin)
11. Indoxyl (3-hydroxyindole) (e.g. indican)
12. Others in which neutral principles are included (e.g. crocin and picrocrocin, gentiopicrin and gentiamarin).

Function of glycosides in plants: They act as sugar reserves, regulating, detoxifying, and defensive roles.

Classification

Glycosides are classified according to:

1. Nature of sugar
2. The chemical nature of aglycone
3. The therapeutic action
4. The glycosides linkage

Classification according to nature of sugar: Glycosides are classified according to nature of sugar and kind of sugar. Glycosides have glucose as a sole sugar. Similar to it pentosides yield pentose. Sugar arabinose and rhamnosides yield the methyl-pentose and rhamnose. Some cardiac glycosides have special sugar component called deoxy or desoxy sugar found only in cardiac glycosides.

Classification according to chemical nature of aglycone group: The classification is based on the chemical nature of the aglycone group such as steroid structure containing glycosides, etc. The main disadvantage of this classification is that it includes all kinds of plant constituents. Anthracene ring containing glycosides, flavone glycosides, cyanogenetic glycosides, alcohol, phenol, aldehyde group containing glycosides, etc.

Various aglycone groups are given in Table 9.2.

Classification according to therapeutic action: This classification offers an excellent opportunity to group together glycosides which show characteristic or selective therapeutic action on a particular organ and/or gainst the particular aliment.

Examples:

1. Digitalis glycosides: Their action of heart/cardiac muscle called cardiac glycosides.
2. Purgative glycosides: Anthraquinone ring with which a definite structure activity relationship act as purgative principle.
3. Bitter glycosides: Glycosides of family gentianaceae because of bitter taste are called bitter glycosides, which show their common use, understood by word bitters.

Table 9.2: Classification of glycosides with examples

Glycosides	Drugs
Cardiac or sterol	Digitoxin, gitoxin, digoxin from digitalis
Anthraquinone or anthracene	Sennosides from senna, cascarosides from cascara, barbolin from aloe.
Saponin glycosides	Glycyrrhizin in glycyrrhiza, diosgenin from discorea.
Cyanogenetic or cyanophoric glycosides	Amydalin—bitter almond Prussian—wild cherry bark
Isothiocyanate glycosides	Sinigrin—black mustard Sinalbin—white mustard
Flavanol glycosides	Rutin—Ruta, Hesperidin—orange, kaempferol—senna
Alcohol glycosides	Salicin—salix
Aldehyde glycosides	Salinigrin—salix
Lactone or coumarin	Skimmin—staranise, aersculin—harsechest nut bean
Miscellaneous	Quassium—quassia, picrotoxin—anamista

Classification based on glycosides linkage: This classification is based on the basis of the linkage which is formed between the aglycone and glycone part. The linkages are formed through oxygen, sulphur, nitrogen or carbon.

Extraction procedure of glucosidal drugs: The extraction of glycosidal drug is performed by continuous hot percolation using soxhlet apparatus with alcohol as a solvent. But before it is required to inactivate the enzymes present in the glycosides for better yield. Thus following methods for activation are:

- Fresh dry material is heated with boiling water or boling alcohol for 10 to 20 min.
- Material is boiled with acetone.
- Material is treated with acid at pH 2 at cold temperature.
- Extract is treated with low temperature.

Stas-otto method:

1. The fresh dry material is coarsely powdered and then enzymes are activated.

2. The extraction is carried out by percolation with mixture of methanol and water due to its solubility pattern.
3. The percolate is again treated with lead acetate to precipitate chlorophyll and tannins and marc is discarded.
4. Again filtrate and residue is obtained by filtration of sample, this filtrate is treated with H_2S gas to remove excess of lead acetates as lead sulphide.
5. Finally filtrate the solution and evaporate filtrate to get glycosidal residue.

Isolation method for glycosidal drug: There are mainly three types of methods are used for it:

1. By different solubility method
2. Fractional crystallization
3. By chromatography

By different solubility method: In this method glycosidal extract is treated with many solvent like mixture of water and methanol and thus glycosides are separate out.

Fractional crystallization: In this method crystal of drug is prepared by isolation method and by crystal formation is separated out.

By chromatography: In chromatography preparative type of TLC is formed in which the different color writing study is performed.

Identification test for glycosidal drugs:

For normal glycosides:

a. *Xanthohydrol test:* The drug is 0.125% of xanthohydrol in glacial acetic acid and 1% HCl and heated red color is observed.
b. *Antimony trichloride test:* Cardinolides are treated with antimony trichloride and trichloroacetic acid blue to violet color is obtained.
c. *Liberman test for steroidal glycosides:* Steroidal glycosides is treated with CCl_4, acetic anhydride and conc. H_2SO_4 violet blue color is obtained.
d. *Tollens test:* Glycosides solution in pyridine is treated with silver paper, the solution liberates silver. The silver causes mirror on wall of test tube.
e. *Legal test:* Glycosides are treated with pyridine (for dissolution), 1 drop of 2% sodium nitroprusside and 1 drop of 20% NaOH deep red color is observed.

Applications:

1. Cardiac stimulants (digitalis)
2. Purgative—laxative (aloe, rhubarb, seena, cascara)
3. Bitter tonics (picrorrhiza)
4. Expectorants (wild cheery)
5. Steriodal drug synthesis (dioscorea)

Cardiac Glycosides

Many of the plants known to contain cardiac or cardiotonic glycosides have long been used as arrow poisons (e.g. *strophanthus*) or as heart drugs (e.g. *digitalis*). They are used to strengthen a weakened heart and allow it to function more efficiently, though the dosage must be controlled very carefully since the therapeutic dose is so close to the toxic dose. In plants, cardiac glycosides are confined to the Angiosperms, but are found in both monocotyledons and dicotyledons.

The therapeutic action of cardioactive glycosides depends on the structure of the aglycone, and on the type and number of sugar units attached. Two types of aglycone are recognized, cardenolides, e.g. digitoxigenin from *Digitalis purpurea* and bufadienolides, e.g. hellebrigenin from *Helleborus niger.*

The cardenolides are more common, and the plant families the apocynaceae (e.g. *strophanthus*), liliaceae (e.g. *Convallaria*), and scrophulariaceae (e.g. *digitalis*) yield medicinal agents. The rarer bufadienolides are found in some members of the liliaceae (e.g. *urginea*) and ranunculaceae (e.g. *helleborus).*

Biosynthesis: Formed through mevalonate and deoxyxylulose pathway.

For cardiac glycosides

a. *Raymond's test:* In this test small amount of glycosides is dissolved in 1 ml of 50% ethanol, then 0.1 ml of 1% solution of dinitrobenzene in ethanol is added with 2–3 drops of 20% NaOH, violet color appears which turn blue after sometime.

   Note: This color is due to the activation of methylene group of C-21 in the lactone ring of cardiac glycosides.

b. *Modified Raymond's test or Kidde's reagent test:* Glycosides treated with Kidde's reagent gives blue violet color. This color disappears after sometime.

c. *Kidde's reagent:* Mix equal quantity of 0.2% solution of 3, 5 dinitrobenzoic acid in 50% methanol and 5.7% w/v of aqueous solution of KOH.

d. *Keller-Kiliani test:* In this test 1 gm of powdered drug is extracted with 10 ml of 70% alcohol, then filtered. 5 ml of filtrate is mixed with 10 ml of H_2O_2 and add 0.5 ml of strong lead acetate due to which precipitate formed and then filtered. Shake filterate with 5 ml of $CHCl_3$ with 1 ml of 1 volume of 5% $FeSO_4$ and 99 volume of glacial acetic acid and then 1–2 drop of concentrated H_2SO_4 is added due to which blue color appears.

   Note: Blue color is formed due to deoxy sugar.

DIGITALIS

Synonyms: English—digitalis, foxglove.

Biological source: **Digitalis is dried** leaves of *Digitalis purpurea* **belonging to family** scrophulariaceae. Dried at not more than 60°C and moisture content not more than 5%.

Habitat: The common foxglove of the woods (*Digitalis purpurea*), is widely distributed throughout Europe and is common as a wildflower in Great Britain, growing freely in woods and lanes, particularly in South Devon, ranging from Cornwall and Kent to Orkney, but not occurring in Shetland, or in some of the eastern counties of England.

Botany:

- *Kingdom:* Plantae
- *Division:* Angiospermae
- *Order:* Lamiales
- *Family:* Plantaginaceae
- *Genus:* Digitalis
- *Species:* Purpurea

Part used: Dried leaflets.

Organoleptic characters: (Fig. 9.14)

- *Color:*
  - Greyish green (lower surface)
  - Dark green (upper surface)
- *Odor:* Characteristic
- *Taste:* Bitter
- *Shape:* Ovate-lanceolate
- *Size:* 10 to 40 cm long, 3 to 10 cm wide

Chemical constituents: Digitalis contains four important glucosides of which three are cardiac stimulants. The most powerful is digitoxin, an extremely poisonous and cumulative drug, insoluble in water, digitalin, which is crystalline and also insoluble in water; digitalin, amorphous, but readily soluble in water, rendering it, therefore, capable of being administered subcutaneously, in doses so minute as rarely

Fig. 9.14: Digitalis purpurea

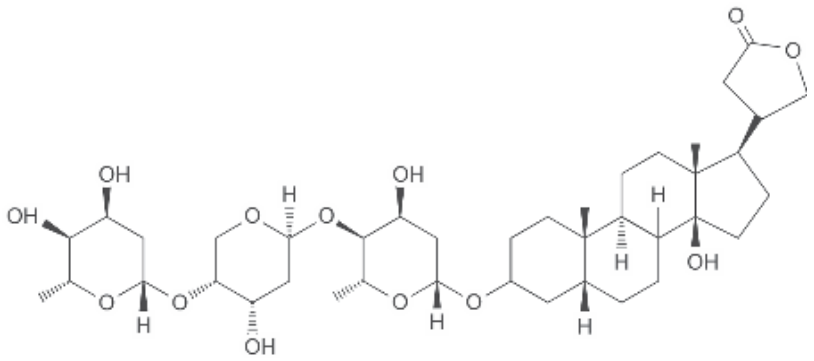


Fig. 9.15: Digitoxin

to exceed of a grain; digitonin, which is a cardiac depressant, containing none of the physiological action peculiar to digitalis, and is identical with saponin, the chief constituent of senega root. Other constituents are volatile oil, fatty matter, starch, gum, sugar, etc. (Fig. 9.15).

Chemical test: Keller-Kiliani test: In this test 1 gm of powdered drug is extracted with 10 ml of 70% alcohol, then filtered. 5 ml of filtrate is mixed with 10 ml of H_2O_2 and add 0.5 ml of strong lead acetate due to which precipitate formed and then filtered. Shake filterate with 5 ml of $CHCl_3$ with 1 ml of 1 volume of 5% $FeSO_4$ and 99 volume of glacial acetic acid and then 1–2 drop of concentrated H_2SO_4 is added due to which blue color appears.

Note: Blue color is formed due to deoxy sugars.

Uses: Digitalis glycosides increase the force of contraction of heart without increasing the oxygen consumption and slow the heart rate when auricular fibrillation is present. To be used only under strict medical supervision. Not used as a herbal drug.

SQUILL

Synonyms: **English:** White squill, squill bulb (European squill), **Hindi:** Chhoti jungli, **Bengali:** Suphadiekhus, **Tamil:** Shirunari.

Biological source: Squill consists of dried slices of the bulb of *Urginea indica* (Indian squill) and *Urginea maritima* (European squill) belonging to family liliaceae.

Habitat: European squillis found in dry, sandy places, especially the seacoast in most of the Mediterranean districts, and is found in Portugal, Morocco, Algeria, Corsica, southern France, whereas Indian squill is found throughout India including konkan and saurashtra.

Botany:

- Kingdom: Plantae
- Order: Asparagales
- Family: Hyacinthaceae
- Genus: *Scilla*
- Species: *Indica*, *maritime*

Part used: Bulb cut into slices, dried and powdered.

Table 9.3: Organoleptic characters of squill

Macroscopic characters	Indian squill	European squill
Color	Yellowish white	Pale yellow
Odor	Slight	Slight
Taste	Bitter and acrid	Bitter, mucilaginous and acrid
Shape	Curved and sickle shaped	Curved strips
Size	1 to 5 cm long, 5 to 10 mm broad	5 to 6 cm long, 3 to 8 mm broad

Chemical constituents: Scilla contains cardiac glycosides scillaren A and B and enzyme scillarenase. Three bitter glucosidal substances, namely scillitoxin, scillipicrin and scillin were isolated. The first two are amorphous and act upon the heart, the former being the more active; scillin is crystalline and causes numbness and vomiting. Other constituents are mucilaginous and saccharine matter, including a peculiar mucilaginous carbohydrate named sinistrin, an inulin-like substance, which yields laevulose on being boiled with dilute acid present in Indian squill (Fig. 9.16).

Chemical test:

1. For cardiac glycosides:
   Keller-Kiliani test: In this test 1 gm of powdered drug is extracted with 10 ml of 70% alcohol then filtered. 5 ml of filtrate is mixed with 10 ml of H_2O_2 and add 0.5 ml of strong lead acetate due to which precipitate formed and then filtered. Shake filterate with 5 ml of $CHCl_3$ with 1 ml of 1 volume of 5% $FeSO_4$ and 99 volume of glacial acetic acid and then 1–2 drop of concentrated H_2SO_4 is added due to which blue color appears.
   Note: Blue color is formed due to deoxy sugars.
2. Mucilage stains reddish purple with iodine water. This test distinguishes between European scilla and Indian scilla.

Uses: Stimulating, expectorant, diuretic, cardiac tonic, acting in a similar manner to digitalis, slowing and strengthening the pulse, though more irritating to the gastrointestinal mucous membrane. On account of its irritant qualities it is not administered in diseases of an acute inflammatory nature. It has also been given as an emetic in whooping-cough and croup, usually combined with ipecacuanha, but as an emetic is considered very uncertain in its action.

Anthracene glycosides or anthraquinone glycosides: They are found abundantly in dicot plant families: Ericaceae, Euphorbiaceae, Leguminoseae, and Rubiaceae. These glycosides contain an aglycone group that is a derivative of anthraquinone.

For anthraquinone glycosides:

a. *Borntrager test:* Powder drug is treated with dil H_2SO_4 and boiled for 5–10 minutes and filtered. The filtrate is shaked with organic solvent (benzene/chloroform). The organic layer is separated and treated with ammonia solution. The ammonical layer appears pink.

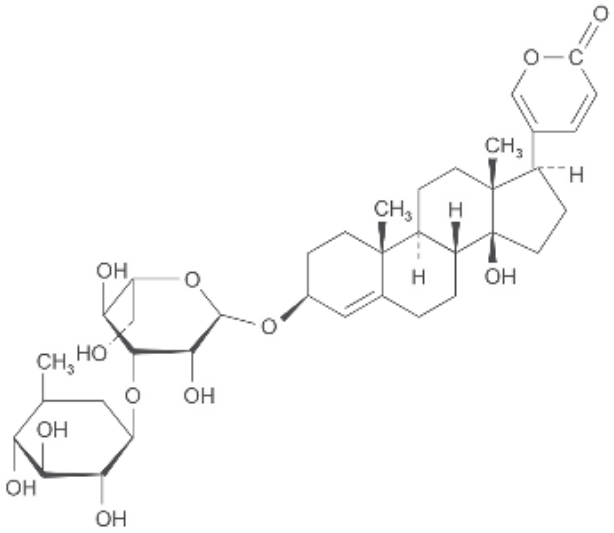


Fig. 9.16: Scillaren A

b. *Modified anthraquinone test:* Powder drug is treated with dil HCl and 5 ml of 5% $FeCl_3$ cooled and shake with organic solvent, the organic layer is treated with ammonia pink, red color is obtained.
Note: Addition of $FeCl_3$ is due to break of C–C linkage of glycosides which is stronger than C = O linkage.

SENNA POD

Synonyms: **Hindi:** Hindisana, **Bengali:** Sonamukhi, **Tamil:** Nila Vakai.

Biological source: Senna pods are dried ripe fruits of *Cassia angustifolia* (Tinnevelly senna pods) and *Cassia acutifolia* (Alexandrian senna pods) belonging to family Leguminosae.

Habitat: Cultivated in dry lands of southern and western India, and indigenous to Arabia.

Fig. 9.17: Senna pod

Botany:

- Kingdom: Plantae
- Division: Angiospermae
- Order: Fabales
- Family: Fabaceae
- Genus: *Senna*
- Species: *C. angustifolia, C. acutifolia*

Part used: Dried leaflets (Folium Sennae), Pods (Fructus Sennae).

Chemical constituents: Tinnevelly senna pods contain approximately 3% dianthrone glycosides (sennosides A-D) whereas Alexandrian senna pods contain approximately 4–5%; anthraquinones including aloe-emodin and rhein 8-glucoside; mucilage; tannins; flavonoids especially kaempferol; and resinous substances. Senna pods contain higher levels of glucosennosides and smaller amounts of anthraquinones glycosides compared with the leaves (Fig. 9.18).

Chemical test:

- Borntrager test is positive due to presence of anthraquinone glycosides. Boil plant material with dilute H_2SO_4, filter and shake with organic solvent (ether or benzene). Separate the organic layer and add ammonia, ammonical layer turns pink or red.
- Ether extract of hydrolysed acid solution of senna with methanolic magnesium acetate solution Alexandrian senna gives pink color in daylight and pale green-orange color in filtered UV light while Tinnevelley senna gives orange color in daylight and yellow-green color in filtered UV light.

Table 9.4: Organoleptic characters of senna

Macroscopic characters	Alexandrian senna	Tinnevelley senna
Color	Green on surface	Brownish green veins
Odor	Faint	Faint
Taste	Slightly bitter	Slightly bitter
Shape	Broadly oblong	Oblong and slightly curved
Size	5 cm long, 2 to 2.5 cm broad	5 cm long, 1.5 to 2 cm broad

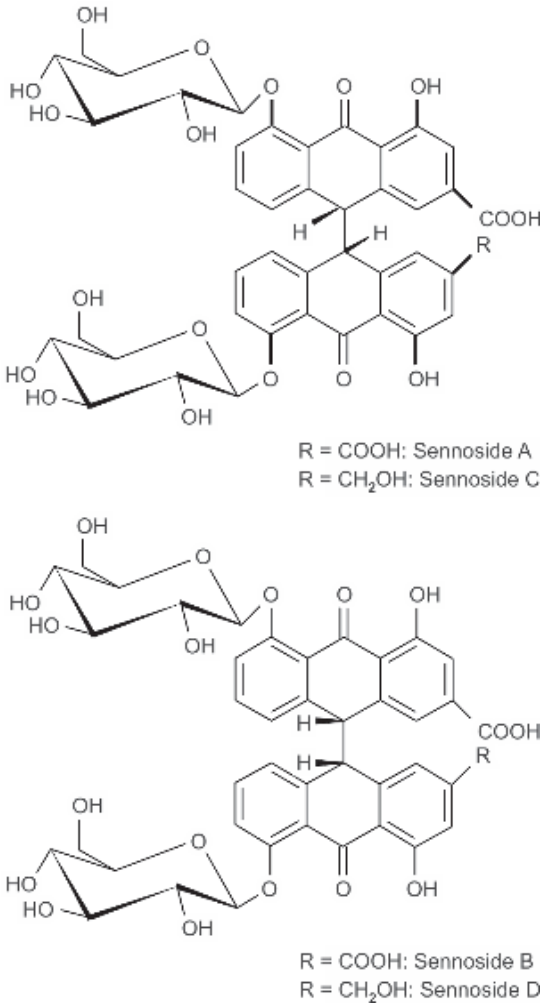


Fig. 9.18: Sennosides

Standards:

- Foreign matter: NMT 1%
- Loss on drying: NMT 12%
- Total ash: NMT 9.0%
- Acid-insoluble ash: NMT 2.0%

Uses: Anal fissures, anti-diarrheal, anti-inflammatory, cellular regeneration, children's laxative, cleansing, constipation, detoxifying, hemorrhoids, laxative, pre- and post-operative cleansing.

SENNA LEAF

Synonyms: Alexandrian Senna, Sene de la palthe, Nubian Senna, Cassia Senna.

Biological source: It consists of dried leaves of *Cassia angustifolia* (Tinnevelly senna) and of *Cassia acutifolia* (Alexandrian senna) belonging to family Leguminosae.

Habitat: Egypt, Nubia, Arabia, Sennar.

Botany:

- Kingdom: Plantae
- Division: Angiospermae
- Order: Fabales
- Family: Fabaceae
- Genus: *Senna*
- Species: *C. angustifolia, C. acutifolia*

Part used: Dried leaflets, pods.

Organoleptic Characters (Fig. 9.19)

Color: Yellowish green.

Odor: Slight.

Taste: Bitter and mucilaginous.

Extra features: Isobilateral leaf with trichomes on both sides. The leaf has asymmetrical base with lanceolate shape.

Microscopy of Senna Leaf

Type: The leaf is isobilateral.

Epidermis: Upper and lower epidermises are similar in appearance; they are composed of cells with thin, straight or slightly sinuous

Fig. 9.19: Senna leaves

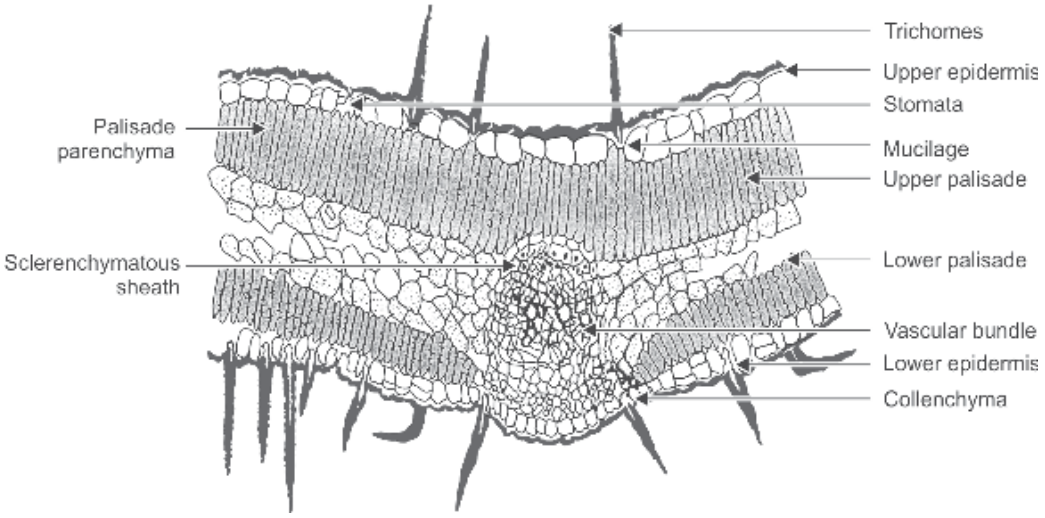


Fig. 9.20: Microscopy of senna leaf

walls, polygonal in outline except in the regions over the veins where they are more elongated and may show faint cuticular striations.

Stomata: Numerous paracytic stomata are present.

Trichomes: The covering trichomes which are found scattered as well as attached to fragments of the epidermises; they are unicellular, conical, with thick and distinctly warted walls.

Calcium oxalate crystals: The calcium oxalate crystals which are very abundant; they occur as prisms in the cells of the parenchymatous sheath surrounding the groups of fibres, and also as cluster crystals of moderate size in the cells of the spongy mesophyll.

Fibres: The fibres, which occur in groups; they are thick-walled, lignified with a few pits and are surrounded by a calcium oxalate prism sheat.

Others: The fragments of the lamina in sectional view showing the palisade under both epidermises; the palisade cells under the upper epidermis are much elongated and more or less straight-walled, whereas those under the lower epidermis are shorter and have distinctly sinuous walls. The rounded spongy mesophyll cells between the two layers of palisade frequently contain cluster crystals of calcium oxalate.

Staining reagents:

Phloroglucinol: HCl-1:1 (Lignified tissues are seen red/pink)

Ruthenium red: Mucilaginous cell of epidermis seen red/pink.

Acetic acid: Crystals are insoluble.

Sudan red III: Cutin/cuticle are seen pink.

Chemical constituents: Senna leaf contains: Approximately 3% dianthrone glycosides (sennosides A, A1, B, C, D, E, F and G); and small amounts of anthraquinones including aloe-emodin and rhein 8-glucoside; approximately 10% mucilage; tannins; and flavonoids.

Chemical test: Borntrager test and modified Borntager test both are positive due to presence of anthraquinone glycosides.

Standards:

- Foreign matter: NMT 1%
- Loss on drying: NMT 12%
- Total ash: NMT 9.0%
- Acid insoluble ash: NMT 2.0%

Uses: Anal fissures, anti-diarrheal, anti-inflammatory, cellular regeneration, children's

laxative, cleansing, constipation, detoxifying, hemorrhoids, laxative, pre- and post-operative cleansing.

Adulterants: Arabian or Bombay Senna, Mecca Senna.

ALOE

Synonyms: Sanskrit: Ghrita kumari, English: Indian aloe, Hindi: Ghik anvar kumari, Gujarati: Kunvar.

Biological source: It consists of dried juice collected by incision of bases of leaves of various species of aloe, *viz Aloe perryi*, *Aloe vera*, *Aloe ferox*, family Liliaceae.

Habitat: Aloes are indigenous to East and South Africa, but have been introduced into the West Indies (where they are extensively cultivated) and into tropical countries, and will even flourish in the countries bordering on the Mediterranean.

Botany:

- Kingdom: Plantae
- Order: Asparagales
- Family: Asphodelaceae
- Genus: *Aloe*
- Species*: A. perryi*, *A. vera*, *A. ferox*

Parts used: Leaves and dried gel.

Chemical constituents: The most important constituents of Aloes are the two Aloins, Barbaloin and Isobarbaloin, which constitute the so-called crystalline Aloin, present in the drug at from 10 to 30 per cent. Other constituents are amorphous Aloin, resin and Aloe-emodin. Aloe contains two classes of Aloins: (1) Nataloins, which yield picric and oxalic acids with nitric acid, and do not give a red coloration with nitric acid; and (2) barbaloins, which yield aloetic acid ($C_7H_2N_3O_5$), chrysammic acid ($C_7H_2N_2O_6$), picric and oxalic acids with nitric acid, being reddened by the acid. This second group may be divided into a-barbaloins, obtained from Barbadoes aloes, and reddened in the cold, and b-barbaloins, obtained from socotrine and zanzibar aloes, reddened by ordinary nitric acid only when warmed or by fuming acid in the cold. Nataloin forms bright yellow scales. Barbaloin forms yellow prismatic crystals. Aloes also contain a trace of volatile oil, to which its odor is due (Fig. 9.22).

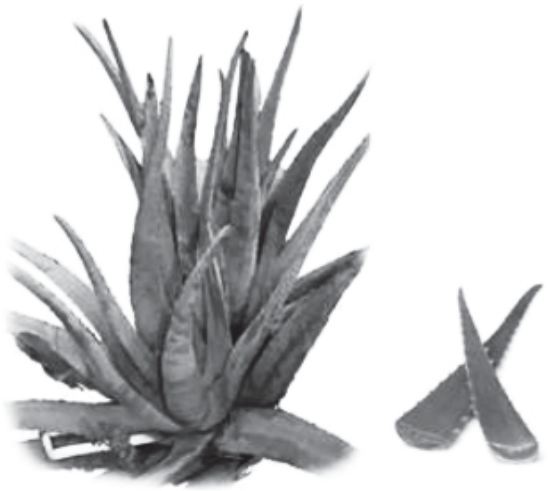


Fig. 9.21: Aloe leaves

Table 9.5: Organoleptic characters of aloe

Characters	Curacao	Socotrine	Zanzibar	Cape
Form	Opaque and translucent	Opaque	Opaque	Transparent and glossy
Color	Reddish brown	Dark brown	Liver color	Dark brown to greenish brown
Fracture	Smooth	Porous	Fairly smooth and porous	Smooth, even and glossy
Odor	Strong and unpleasant	Slight and disagreeable	Pleasant	Unpleasant
Taste	Disagreeable bitter	Disagreeable bitter	Disagreeable bitter	Disagreeable bitter

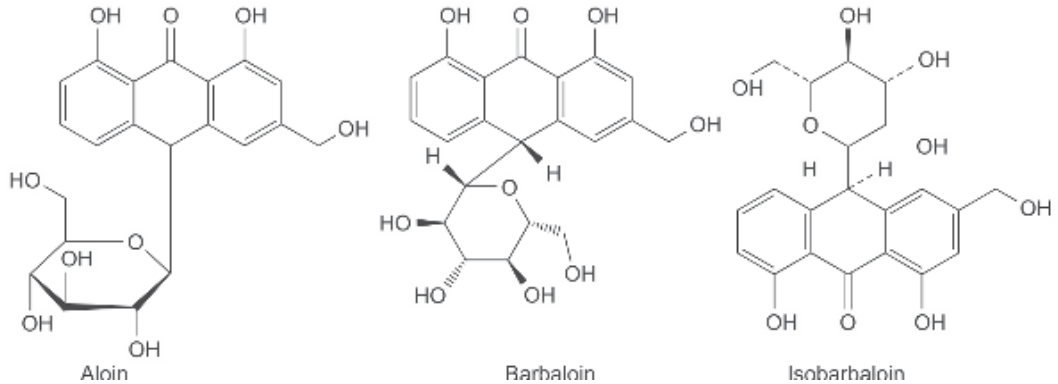


Fig. 9.22: Chemical constituents of aloe

Chemical test: Boil plant material with 5 ml dilute HCl and 5 ml $FeCl_3$, filter and shake with organic solvent (ether or benzene). Separate the organic layer and add dilute ammonia, ammonical layer turns pink or red.

Uses: Aloe has been used for its healing properties, and both oral intake and topical dressings include blisters, insect bites, rashes, sores, herpes, urticaria, athlete's foot, fungus, vaginal infections, conjunctivitis, sties, allergic reactions, and dry skin. Other topical uses include acne, sunburn, frostbite (it appears to prevent decreased blood flow), shingles, screening out X-ray radiation, psoriasis, preventing scarring, rosacea, warts, wrinkles from aging, and eczema.

Adulterants: Natal aloes, Mocha aloes, black catechu and pieces of iron and stones.

RHUBARB

Synonyms: **Sanskrit:** Amlavetusa, **English:** Himalayan rhubarb, **Hindi:** Revand Chini, **Bengali:** Rheuchini, **Tamil:** Variyattu.

Biological source: It consists of dried rhizomes of *Rheum emodi*, family polygonaceae.

Habitat: It is found in Astore, Nagar, Nalter, Ishkomen, mostly rocky and sandy places where moisture remains for a long time.

Botany:

- Kingdom: Plantae
- Family: Polygonaceae
- Genus: *Rheum*
- Species: *R. emodi*

Part used: Rhizome, roots

Organoleptic Characters (Fig. 9.23)

Color: Yellowish brown.

Odor: Fragnant.

Taste: Bitter and astringent.

Shape: Somewhat cylindrical, barrel shaped/conical.

Size: 2–20 cm in length, 1.5–8 cm in dia.

Fig. 9.23: Rhubarb

Extra features: Outer surface is irregular and wrinkled, transverse wrinkles and annulations are present.

Microscopy of Rhizome of Rhubarb (Fig. 9.24)

Parenchyma: The parenchyma cells are thin-walled, elongated cells tapering at the ends. These cells are filled with starch in longitudinal view.

Medullary rays: They composed of cells with slightly thickened walls and both the walls and the cell contents are deep brownish-yellow.

Ground tissue: It is composed of cells varying from rounded to oval to rectangular in outline, they are filled with starch granules or with large cluster crystals of calcium oxalate.

Calcium oxalate: The cluster crystals of calcium oxalate found scattered and in some of the parenchymatous cells.

Starch granules: The starch granules are simple, spherical and compound with distinct, central hilum in the form of a cleft or radiating split.

Vessels: The *vessels,* are large, reticulately thickened and do not give a reaction for lignin occur singly or in small groups and are frequently found in fragments.

Chemical constituents: It consists of anthraquinone derivatives such as chrysophanic acid, emodin, aloe-emodin, rhein and physcion, with their O-glycosides such as glucorhein, chrysophanein, glucoemodin; sennosides A–E, reidin C and others. It also contains d-catechin and epicatechin gallate, with various cinnamoyl and coumaroyl golloyl glucosides and fructoses. Stilbene derivatives, related stilbene glycosides present in other types drug also have volatile oil, containing diisobutyl phthalate, cinnamic and ferulic acids; rutin, fatty acids, calcium oxalate etc. (Fig. 9.25).

Chemical test:

- It gives red coloration with 5.0% NaOH
- It gives pink color with ammonia
- It give Borntrager test positive
- Under ultraviolet radiation *Rheum emodi* gives brown color and *Rheum rhaponticum* gives violet color.

Standards:

- **Total ash:** NMT 7.0%
- **Acid insoluble ash:** NMT 4.0%

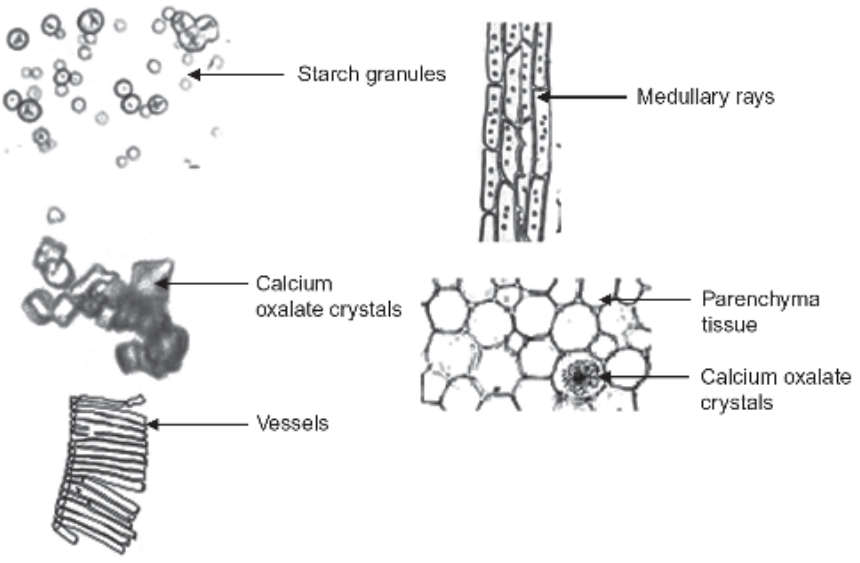


Fig. 9.24: Microscopy of rhizome of rhubarb

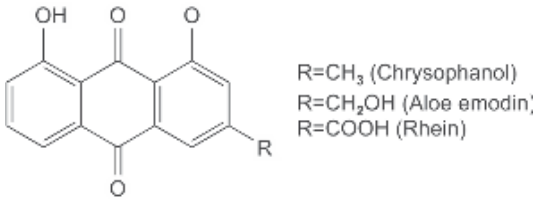


Fig. 9.25: Chemical constituents of aloe

- **Alcohol soluble extractive:** NMT 19.0%
- **Water soluble extractive:** NMT 12.0%

Uses: The root are astringent, tonic and purgative. The tuber is pungent, bitter, alexiteric, emmenagogue, diuretic; reported to be useful in biliousness, chronic bronchitis asthma, sore eyes and bruises. **Locally**, roots are used to chronic constipation. The tuber is used in biliousness, sore eyes and fever. It is also used as blood purifier.

Adulterants: *Rheum rhaponticum* is an adulterant of the official drug.

CASCARA BARK

Synonyms: English: Buckthorn.

Biological source: It is obtained from dried bark of *Rhamnus purshiana* belonging to family Rhamnaceae.

Habitat: Native to Europe; introduced in Kashmir, Himachal Pradesh, Bhutan and the Nilgiris.

Botany:
- Kingdom: Plantae
- Family: Rhamnaceae
- Genus: *Rhamnus*
- Species: *Purshiana*

Part used: Bark

Organoleptic Characters (Fig. 9.26)

Color: Pale black to brown in color.

Shape: Quilled, channeled or flat pieces

Size: 20 cm long, 1 to 4 mm thick.

Fracture: Short and granular

Chemical constituents: The bark contains up to 8–10% of a complex mixture of anthraquinone glycosides of which 60–70% are cascarosides A, B, C and D, other glycosides in minor concentrations include chrysanol, frangulin, barbaloin, glycosides based on aloe-emodin, emodin, chrysophanol and emodinoxanthrone, dianthrones, and free aglycones. The bark also contains barbaloin and O-glycosides of emodin (e.g. frangulin), emosin oxanthrone and palmidin A, B, and C (also found in Rhubarb root). The bark also contains linoleic acid, myristic acid and syringic acid. The bark also contains resins, tannins and lipids. Cascarosides A and B are aloin O- and C-glycosides) and cascarosides C and D are deoxyaloin O- and C-glycosides.

Fig. 9.26: Cascara bark

Chemical test: With 5% KOH it shows red color.

Uses: Stool-softener, non-habit forming stimulant laxative, pancreatic stimulant.

Used for dyspepsia and habitual constipation.

Adulterants: *Frangula bark.*

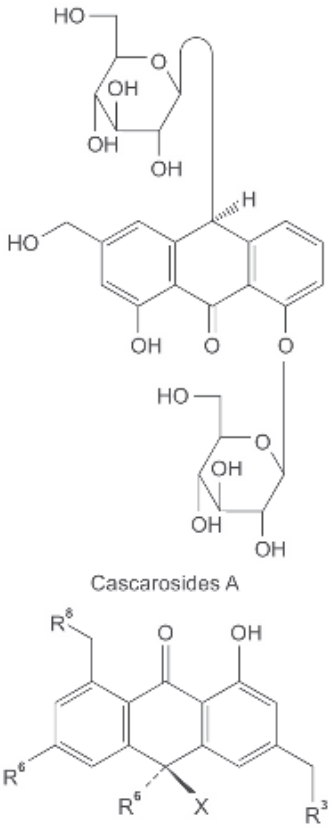
SAPONIN GLYCOSIDES

Steroidal saponins widely distributed in nature. They possess some common characteristics:

A. They produce foam in aqueous solution

B. They cause hemolysis of RBC.

Aglycone of the saponin glycosides is known as sapogenins. They are found in many monocotyledon families, especially the Dioscoreaceae (e.g. *Dioscorea*) and the Liliaceae



	X	Y	R^3	R^6	R^8
Aloin A	Glc	H	OH	H	H
Aloin B	H	Glc	OH	H	H
Cascaroside A	Glc	H	OH	H	Glc
Cascaroside B	H	Glc	OH	H	Glc
Cascaroside C	Glc	H	H	H	Glc
Cascaroside D	H	Glc	H	H	Glc
Cascaroside E	Glc	H	H	OH	Glc
Cascaroside F	H	Glc	H	OH	Glc
Chrysaloin A	Glc	H	H	H	H
Chrysaloin B	H	Glc	H	H	H

Fig. 9.27: Chemical constituents of cascara bark

(e.g. *smilax, trillium*), e.g. dioscin (*dioscorea)*. Acid hydrolysis of dioscin liberates the aglycone diosgenin.

Biosynthesis: Formed through mevalonate and deoxyxylulose pathway.

Test for saponin: About 2 g of the powdered sample was boiled in 20 ml of distilled water in a water bath and filtered. 10 ml of the filtrate was mixed with 5 ml of distilled water and shaken vigorously for a stable persistent froth. The frothing was mixed with 3 drops of olive oil and shaken vigorously, then observed for the formation of emulsion.

DIOSCOREA

Synonyms: **English:** Wild Yam, Greater Yam, Asiatic Yam.

Biological source: It is obtained from root and rhizomes of various discorea species, viz. *D. atropurpurea* Roxb, *D. globosa* Roxb, *D. purpurea* Roxb and *D. deltoidea* belonging to family *Dioscoreaceae.*

Habitat: Native to East Asia; cultivated in Assam, Vadodara, Tamil Nadu, Bengal and Madhya Pradesh.

Botany:

- Kingdom: Plantae
- Family: *Dioscoreaceae*
- Genus: *Dioscorea*
- Species: *Deltoidea*

Parts used: Root and rhizomes.

Organoleptic Characters (Fig. 9.28)

Color: Sightly brown

Taste: Acrid

Odor: None

Shape: Long, branched, crooked and woody.

Fig. 9.28: Dioscorea

Extra features: The therapeutical value is lost after the first year, so that it should be freshly gathered and carefully dried each year.

Chemical constituents: The main bioactive components of wild yam are the saponin, diosgenin, and the alkaloids, dioscorin and dioscorine. It also contains anthocyanins, cyanidin and peonidin-3-gentiobioside acylated with sinapic acid. Much saponin has been found in the roots, and a substance improperly called dioscorein, obtained by precipitating the tincture with water.

Uses: Wild yams are used as cholagogue, anti-spasmodic, anti-inflammatory, antirheumatic, diuretic. Also used for painful periods, cramps and muscle tension. Diosgenin obtained from dioscorea species was used in the first commercial production of oral contraceptives, topical hormones, systemic corticosteroids, androgens, estrogens, progestogens and other sex hormones.

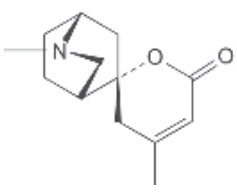


Fig. 9.29: Dioscorin

SHATAVARI

Synonyms: English: Satavari, Hindi: Shakakul, Gujarati: Satavar.

Biological source: Satavari consists of dried roots of *Asparagus racemosus*, belonging to family liliaceae.

Habitat: Shatavari is a perennial much branched climbing herb found all over India, especially in tropical and sub-tropical parts and in Himalayan region up to 1400 m. elevation.

Botany:

- Kingdom: Plantae
- Order : Asparagales
- Family: Asparagaceae
- Genus: *Asparagus*
- Species*: A. racemosus*

Part used: Fleshy roots and leaves

Organoleptic Characters (Fig. 9.30)

Color: Leaves are green, roots are white to buff color sometimes pale brownish.

Odor: Odorless

Taste: Bitter

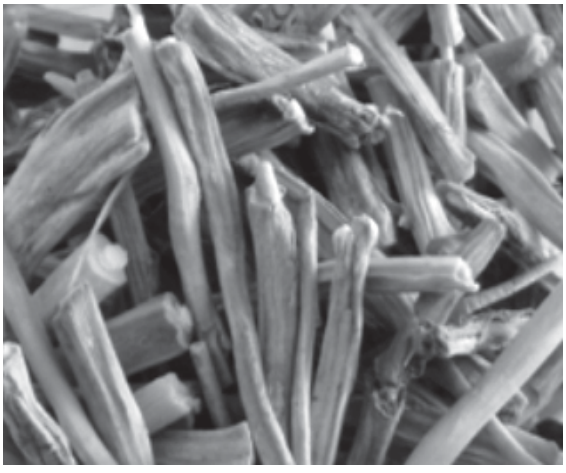


Fig. 9.30: Shatavari

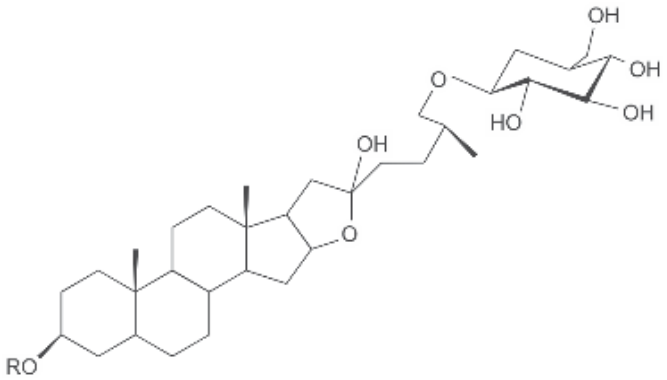


Fig. 9.31: Shatavarin

Shape: Roots are fascicled at the stem base, smooth tapering at both ends.

Size: Tuberous succulent roots are 30 cm to a metre or more in length.

Extra features: Entire roots are tapering on both ends, drug swells when soaked in water and becomes soft and flaccid.

Chemical constituents: Root contains 4 steroidal saponins shatavarins I–IV, water soluble constituents 52.1/2%, moisture 1%, glucose 7% and ash from dried root 4%.

Chemical test: Shake drug with water persistent foam is observed.

Uses: The roots of *Asparagus racemosus* (Shatavari) is a nutritive, aphrodisiac, astringent, used in treatment of general debility, male infertility (due to low sperm count), loss of libido, epilepsy (fits), mental debility and in many male diseases. It is also used in female ailments such as menopausal syndrome, anemia, lower quantity of breast milk secretion, and for both mental and physical ailments.

GINSENG

Synonyms: English: Ginseng

Biological source: Ginseng consists of dried roots of *Panax ginseng* (Asian ginseng) or *Panax quinquefolius* (American ginseng), belonging to family Araliaceae.

Habitat: Ginseng is now found throughout the world.

Botany:

- Kingdom: Plantae
- Family: Araliaceae
- Genus: *Panax*
- Species: *Ginseng, quinquefolius*

Part used: Roots.

Organoleptic Characters (Fig. 9.32)

Asian ginseng: It is an herbaceous perennial plant from 30 to 80 cm high with divided

Fig. 9.32: Ginseng roots

palmate leaves and clusters of red berries in the autumn.

American ginseng: The herbaceous perennial plant grows to a height of twelve to twenty-four inches and has three compound leaves, with five toothed leaflets, that are joined at the top of an erect stem. Greenish-white flowers bloom in late spring or early summer. Green berries follow and ripen to red by late summer.

Chemical constituents: The main bioactive components of ginseng are a diverse group of steroidal saponins called ginsenosides. The triterpenoid saponins referred to collectively as ginsenosides or panaxosides (Fig. 9.33).

Uses: Ginseng is used to relieve stress, increase energy, and improve mental acuity. It has been used to increase physical endurance and lessen fatigue, to improve the ability to cope with stress, and to improve concentration. It is also used for anemia, diabetes, gastritis, neurasthenia, erectile dysfunction, impotence and male fertility, fever, hangover, and asthma. Panax ginseng is also used for bleeding disorders, loss of appetite, vomiting, colitis, dysentery, cancer, insomnia, neuralgia, rheumatism, dizziness, headache, convulsions, disorders of pregnancy and childbirth.

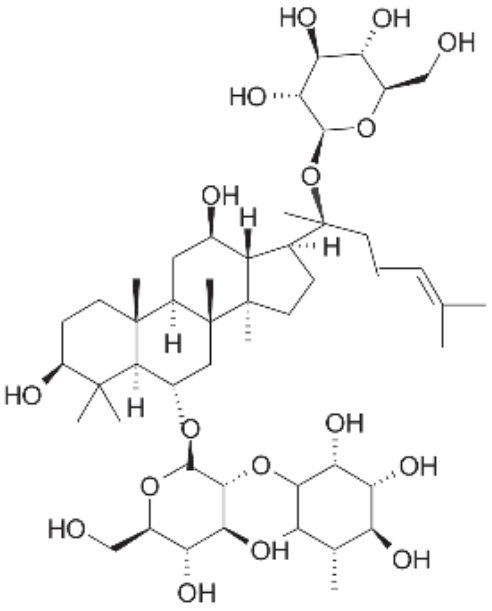


Fig. 9.33: Ginsenosides

METHI SEEDS

Synonyms: Sanskrit: Medhika, English: Fenugreek, Gujarati: Methi, Telugu: Mentulu.

Biological source: It is obtained from seeds of *Trigonella foenum-graecum* belonging to family fabaceae.

Habitat: Indigenous to the countries on the eastern shores of the Mediterranean. It is cultivated in India, Africa, Egypt, Morocco, and occasionally in England.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Order : Fabales
- Family: Fabaceae
- Genus: *Trigonella*
- Species: *T. foenum-graecum*

Parts used: Seeds, pods and leaves.

Organoleptic Characters

Color: Yellow hard seeds

Odor: Strong and characteristic

Taste: Strong

Shape: Irregularly rhomboidal, flattened

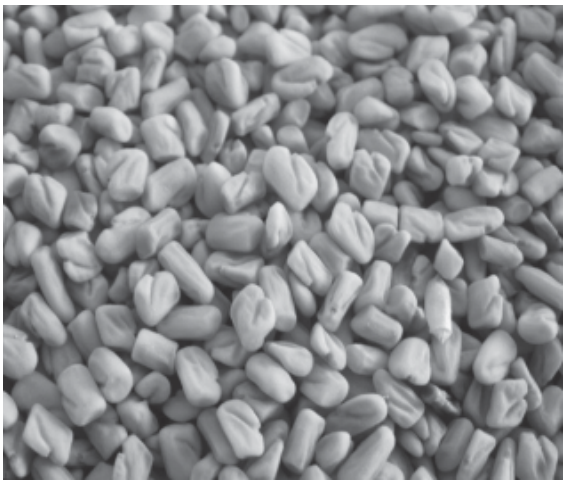


Fig. 9.34: Fenugreek

Chemical constituents: It contains 28% mucilage, 5% stronger-smelling bitter fixed oil, 22% proteids, it also contains two alkaloids, trigonelline and choline, and a yellow coloring substance. It is rich in phosphates, lecithin and nucleoalbumin, considerable quantities of iron in an organic form.

Chemical test: The chemical test of alkaloids, glycosides and steroids can be performed.

Uses: Externally it is used as a poultice for abscesses, boils, carbuncles, etc. It can be employed as a substitute for cod-liver oil in scrofula, rickets, anemia, debility following infectious diseases. The ground seeds are used also to give a maple-flavouring to confectionery and nearly all cattle like the flavour of fenugreek in their forage. The powder is also employed as a spice in curry.

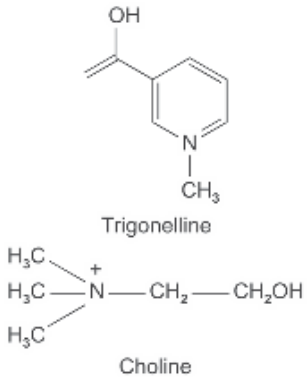


Fig. 9.35: Chemical constituents of fenugreek

GOKHARU

Synonyms: Large gokhru Hindi: Farib duti, Bengali: Bara gokhru, Gujarati: Kadva gokhru.

Small Gokhru Sanskrit: Ikshugandha, English: Small gokhru, Hindi: Chota gokhru, Bengali: Gokhuri.

Biological source: Large gokhru consists of dried ripe fruits of *Pedalium murex* belonging to family pedaliaceae. Small gokhru consists of dried ripe fruits of *Tribulus terrestris* belonging to family Zygophyllaceae.

Habitat: Throughout India, Gujarat, Sri Lanka, Africa, etc.

Botany:

- Kingdom: Plantae
- Family: Pedaliaceae, zygophyllaceae
- Genus: *Pedalium, Tribulus*
- Species: *P. murex, T. terrestris*

Parts used: Whole plant, fruits and seeds.

Table 9.6: Organoleptic characters of large and small gokhru

Parameters	Large gokhru	Small gokhru
Color	Brown	Yellowish white
Shape	Pyramid ovoid shape tapering at base	Globose
Surface	Each fruit has four spines and does not show separate cocci	Spiny having five woody cocci and coccus which contain several seeds

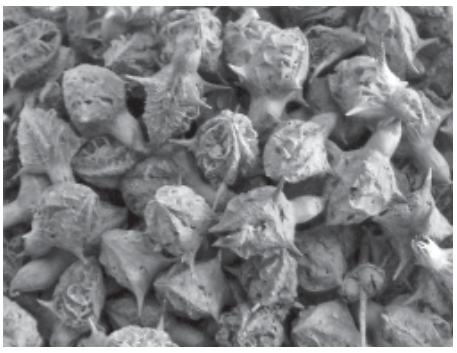


Fig. 9.36: Large gokhru

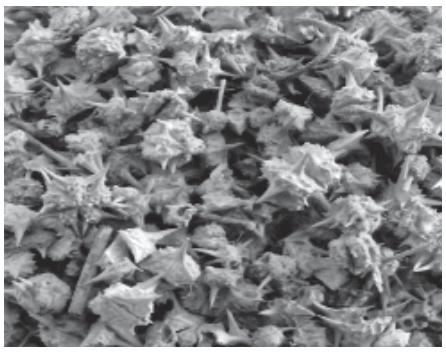


Fig. 9.37: Small gokhru

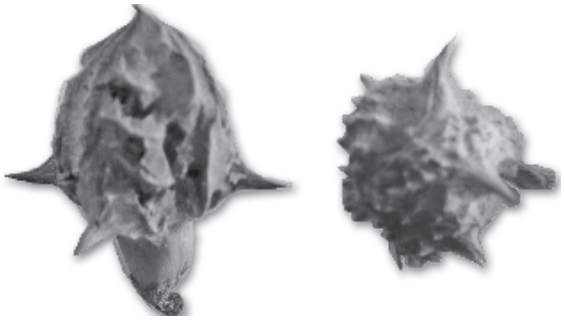


Fig. 9.38: Comparison of large and small gokhru

Chemical constituents: It consists of saponins which on hydrolysis yield diosgenin, ruscogenin and gitogenin. It also contains three flavone glycosides, traces of alkaloids, fixed oil and potassium nitrate.

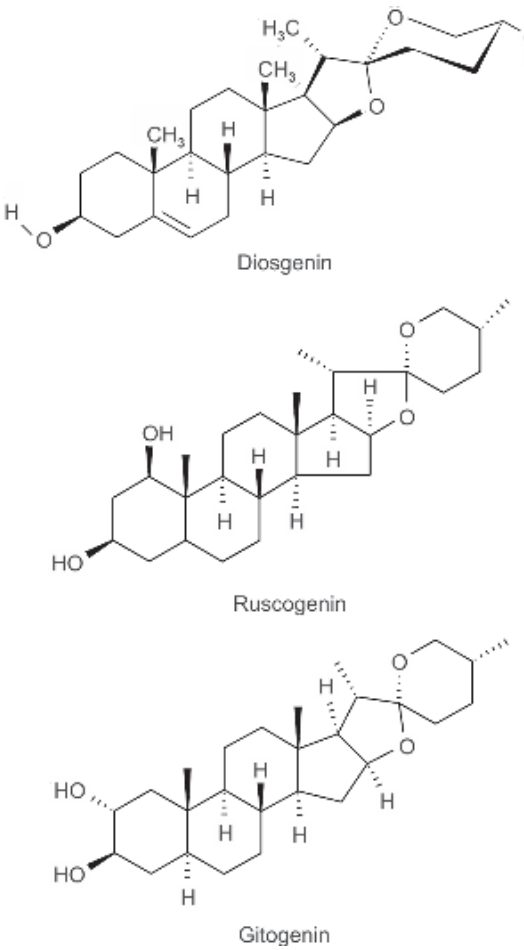


Fig. 9.39: Chemical constituents of gokhru

Uses:

- *Bara gokhru:* Leaves are antibilious. Seeds are demulcant, diuretic, tonic, muscilaginous and aphrodesiac. Used in male impotence, gonorrhoea, and incontinence.
- *Chotta gokhru:* The roots and fruits are sweet, coling, emollient, appetizer, alternate, laxative, cardiotonic, styptic, lithontriptic and tonic. They are useful in strangury, dysuria, vitiated conditions of vat and pitta, renal and vesical calculi, anorexia, dyspepsia, helminthiasis, cough, asthama. The seeds are astringent, strengthening and are useful in epistaxis, hemorrhages and ulcerative stomatitis. The ash of the whole plant is good for external application in rheumarthritis.

Triterpeniod saponins

GLYCYRRHIZA

Synonyms: **Sanskrit:** Yashti-madhu, **English:** Sweetwood, Liquorice, **Hindi:** Mithilakdi, Mulathee.

Biological source: It consists of dried, peeled or unpeeled roots and stolons of *Glycyrrhiza glabra*, belonging to family leguminosae.

Habitat: Natives of South-east Europe and South-west Asia.

Fig. 9.40: Liquorice root

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Fabales
- Family: Fabaceae
- Genus: *Glycyrrhiza*
- Species: *G. glabra*

Part used: Roots.

Organoleptic Characters

Color:

- *Unpeeled:* Yellowish brown to dark brown.
- *Peeled:* Pale yellow.

Odor: Faint and characteristic.

Taste: Sweet, free from bitterness.

Fracture: Fibrous

Extra features: Peeled drug is fibrous and angular in shape.

Microscopy of Liquorice Root

Cork: Fairly abundant, polygonal fragments of orange-brown cork composed of thin-walled cells.

Starch: The abundant starch granules, most of which are simple; they are rather small, spherical to ovoid and slightly flattened; a slit-shaped hilum is visible in some of the larger granules.

Fibres: The very abundant fibres which occur in groups surrounded by a calcium oxalate prism sheath.

Vessels: The vessels, which are found singly or in small groups; some of the individual vessels are very large and are frequently found fragmented. The larger vessels are usually accompanied by lignified xylem parenchyma composed of moderately thin-walled cells, square to elongate rectangular in outline with variably pitted walls.

Calcium oxalate: The prisms of calcium oxalate are fairly uniform in size and occur in the cells forming the crystal sheath surrounding the fibres.

Parenchyma cells: The abundant thin-walled parenchyma from the cortex, medullary rays and pith, the cells vary from rounded to rectangular in outline and are usually filled with starch granules.

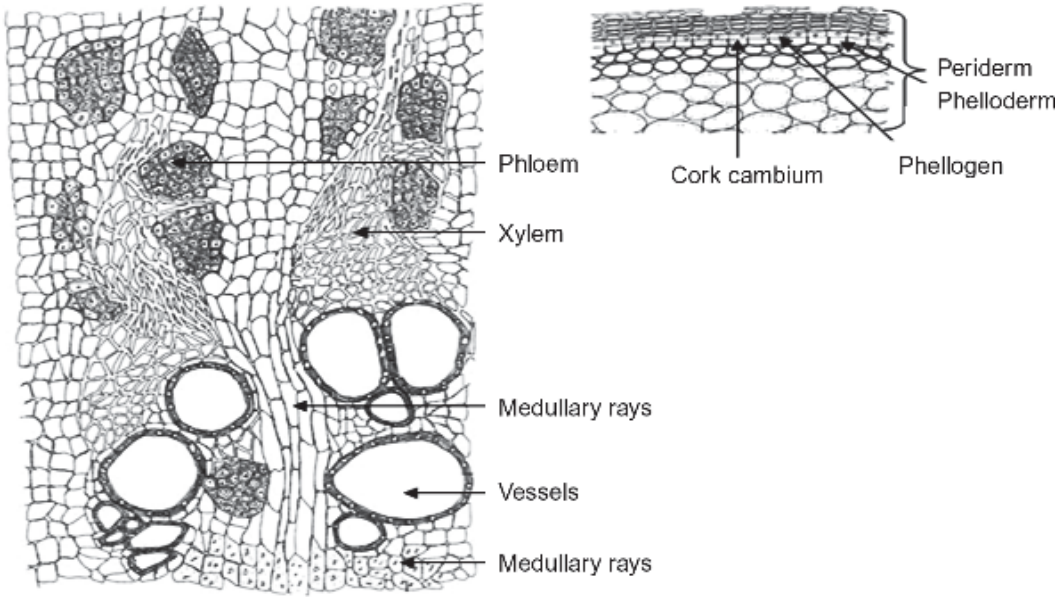


Fig. 9.41: TS of liquorice root

Sieve tissue: Occasional groups of sieve tissue, composed of very thin-walled cells with faint sieve areas, may be found associated with the medullary rays. A small amount of collenchyma is also present.

Staining reagents

Phloroglucinol: HCl-1:1 (lignified tissues are seen red/pink)

Acetic acid: Crystals are insoluble

Iodine solution: Starch (blue)

Sulphuric acid: Calcium oxalate crystals are seen.

Chemical constituents: The chief constituent of liquorice root, to which its sweet taste is due, is glycyrrhizin (6 to 8 per cent), obtainable in the form of a sweet, white crystalline powder, consisting of the calcium and potassium salts of glycyrrhizic acid. The drug also contains sugar, starch (29 per cent), gum, protein, fat (0.8 per cent), resin, asparagin (2 to 4 per cent), a trace of tannin in the outer bark of the root, yellow coloring matter, and 0.03 of volatile oil.

Chemical test:

Test for phenolics: Aqueous extract treated with $FeCl_3$ gives dark coloration.

Test for flavonoids: Aqueous extract treated with mineral acid (HCl/H_2SO_4) gives reddish orange coloration which disappears after addition of alkali and reappears again.

Test for saponin: Powder treated with water gives persistent foam.

Standards:

- Foreign matter: Powdered glycyrrhiza shows no stone cells.
- Loss on drying: NMT 12%
- Total ash: NMT 7.0%
- Acid insoluble ash: NMT 2.0%

Uses: Powdered liquorice root is an effective expectorant, and has been used for this purpose since ancient times, especially in Ayurvedic medicine where it is also used in tooth powders and is known as Jastimadhu. Modern cough syrups often include liquorice extract as an ingredient. Additionally, liquorice may be useful in conventional and naturopathic medicine for both mouth ulcers and peptic ulcers

Adulterants: Indian liquorice (*abrus pracatorious*).

BRAHMI

Synonyms: **English:** Water Hyssop, **Tamil:** Nirbrahmi, **Gujarati:** Jalanevari.

Biological source: It is obtained from the herb of *Bacopa monnieri* belonging to family scrophulariaceae.

Habitat: Brahmi is a perennial creeping herb with small white flowers. Its leaves are bright green and look almost like a succulent. It grows in damp, marshy areas, in both fresh and brackish water. It is commonly found throughout Southeast Asia, but has since migrated with great success to Florida and several other southern states in the US. Because of its easy adaptability, it is a favorite foliage for aquariums both big and small.

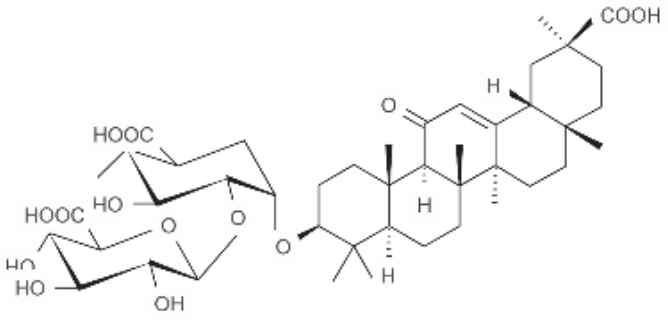


Fig. 9.42: Glycyrrhizin

Botany:

- Kingdom: Plantae
- Family: Scrophulariaceae.
- Genus: *Bacopa*
- Species: *Monnieri*

Part used: Whole plant.

Organoleptic Characters (Fig. 9.43)

Leaves: The succulent leaves are sessile, opposite, decussate, obovate-oblanceolate in shape, 1.0–2.5 cm × 0.4–1.0 cm in size.

Flowers: The flowers are small and white, with four or five petals. Its ability to grow in water makes it a popular aquarium plant.

Stem: 10 to 30 cm long rooting at nodes, branches numerous ascending.

Fig. 9.43: Brahmi

Chemical constituents: The active principle is alkaloids brahmine (0.1–0.2%) and hersaponin in leaves. It also contains bacoside A and bacoside B, betulic acid, β sitosterol and stigmasterol.

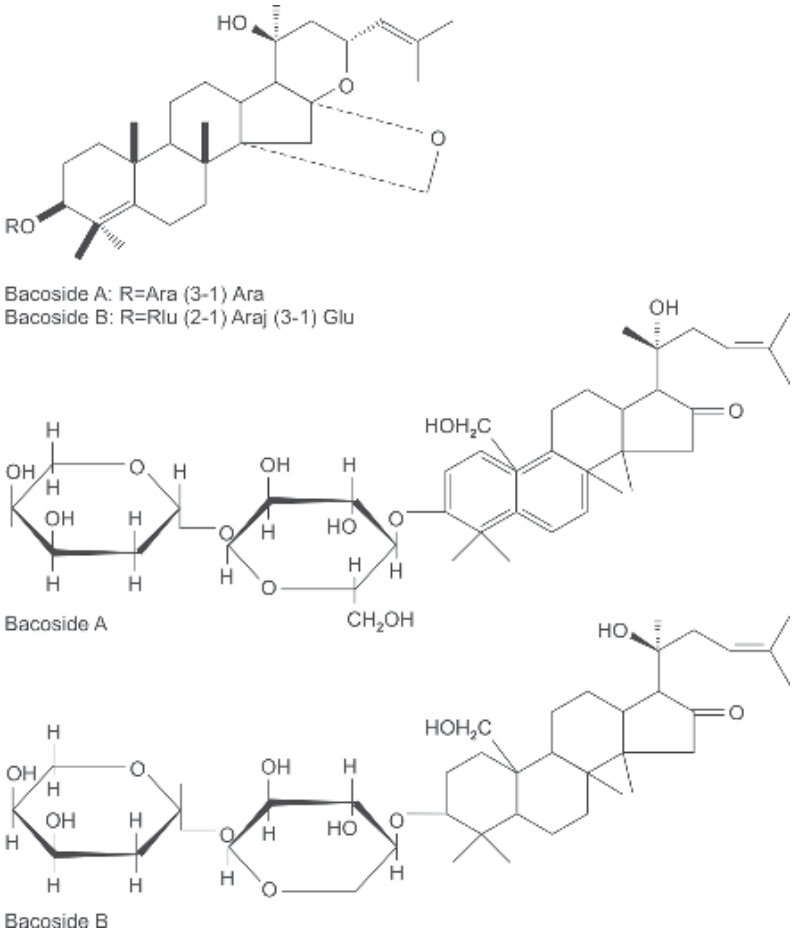


Fig. 9.44: Chemical constituents of brahmi

Uses: Brahmi has antioxidant properties. It has been reported to reduce oxidation of fats in the blood stream, which is a risk factor for cardiovascular diseases. It has been used for centuries to help benefit epilepsy, memory capacity, increase concentration, and reduce stress-induced anxiety. It is listed as a nootropic, a drug that enhances cognitive ability. **In Ayurveda—**it is bitter, pungent, heating, emetic, laxative and useful in bad ulcers, tumours, ascites, enlargement of spleen, indigestion, inflammations, leprosy, anaemia, biliousness, etc.

In unani system of medicine: It is bitter, aphrodisiac, good in scabies, leucoderma, syphilis, etc. It is promising blood purifier and useful in diarrhea and fevers.

ARJUNA BARK

Synonyms: **Sanskrit:** Arjuna, **English:** Arjuna Myrobalan, **Hindi:** Arjun, Kahu, **Gujarati:** Sajadan.

Biological source: Arjuna is dried bark of *terminalia arjuna*, family combretaceae.

Origin: *Terminalia arjuna* is common throughout India especially in the sub-Himalayan tracts and Eastern India.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Myrtales
- Family: Combretaceae
- Genus: *Terminalia*

Species: *Arjuna*

Organoleptic Characters

Color: Externally it is pink or flesh colored with mealy coating and internal surface is reddish brown.

Odor: None

Taste: Gritty and astringent

Fracture: Fibrous

Fig. 9.45: Arjuna bark

Size: Varying size with 5 to 10 mm thickness (Fig. 9.45).

Extra features: 40 meter high deciduous tree. Leaves are simple, 4–6″ long oppositely arranged, rectangular or oval. At the base of the lamina two glands are present. Flower: Green and star-like spikes, calyx smooth. Fruit: Truncate.

Chemical constituents: The bark contains specific medicinal active constituents, namely triterpene glycosides like arjenetosides I, II, III, IV, arjunine and arjunetin. It is also rich in saponins, natural antioxidants (flavonoids—arjunone, arjunolone, leteilin) gallic acid, ellagic acid, oligomeric proanthocyanidins, phytosterols, rich in minerals like calcium, magnesium, zinc and copper.

Chemical test:

Fluorescence analysis: The fluorescence analysis is carried out with 10% extract of ether and petroleum ether in UV chamber.

Table 9.7: Comparative chemical test

Phytosomes	Source	Use
Chemicals	*T. arjuna*	*T.tomentosa*
Ether	Pinkish white	Pale blue
Petroleum ether	Bright pinkish red	Pale white blue

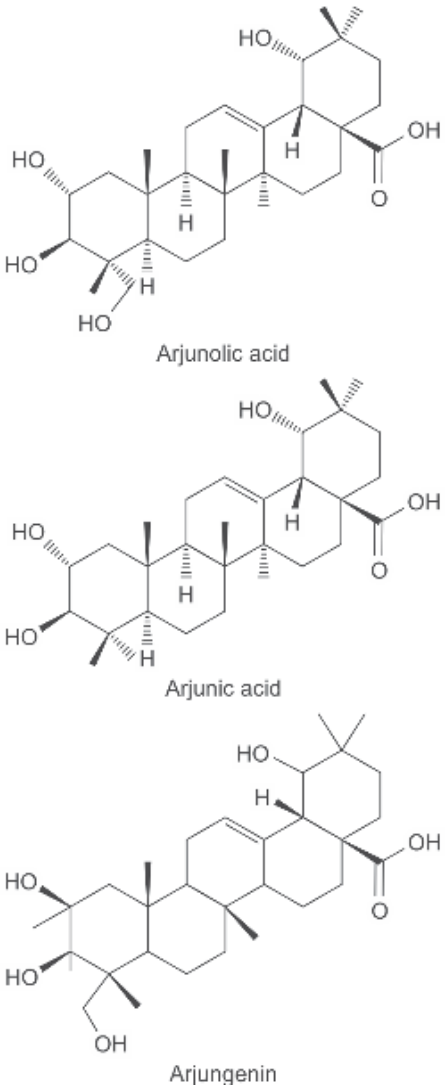


Fig. 9.46: Chemical constituents of arjuna bark

Uses: The bark is astringent, sweet, acrid, cooling, aphrodisiac, cardiotonic, urinary astringent, expectorant, alexiteric and is useful in fractures, ulcers, cirrhosis of the lever, hyperhidrosis, otalgia and hypertension.

Adulterants: *Terminalia tomentosa* (dried bark). It is distinguish by Arjuna bark by fluorescence test.

SENEGA

Synonyms: Senega root, Senega snake root, Radix senegae, Rattlesnake root.

Biological source: Senega consists of dried roots and root stocks of *Polygala senega* linn and *Polygala chinensis* belonging to family Polygalaceae.

Habitat: North western USA, India (Indian Senega).

Botany:

- Kingdom: Plantae
- Family: Polygalaceae
- Genus: *Polygala*
- Species*: Senega*

Parts used: Roots and root stocks.

Organoleptic Characters

Color: Grayish brown to yellowish brown.

Odor: Characteristic resembling methyl salicylate.

Taste: First sweet then bitter, acrid and irritating.

Shape: Longitudinal stratified.

Size: Length 5 to 20 cm, diameter 2 to 12 cm (Fig. 9.47).

Chemical constituents: Triterpenoid saponins, senegin, polygalic acid, sapogenin, sengins, phenolic acids, methyl salicylate and polygalitol.

Fig. 9.47: Senega root

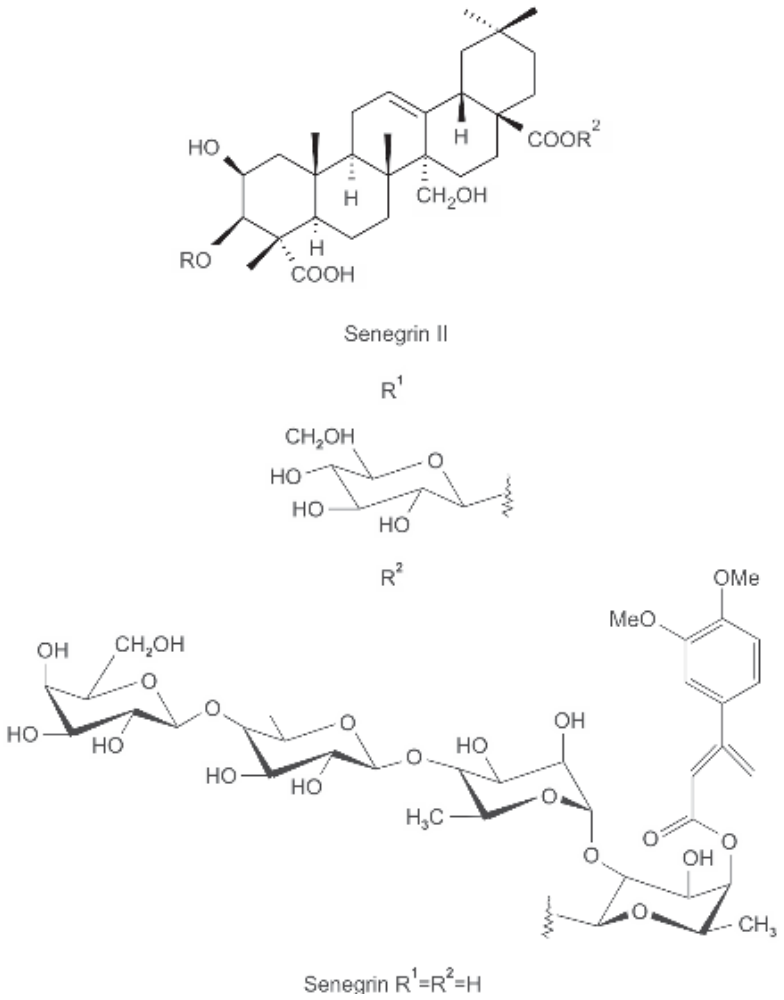


Fig. 9.48: Chemical constituents of senega

Chemical test: Shake drug with water, persistent foaming is seen.

Uses: It is used in bronchitis, asthma, tracheitis, emphysema and inflammation of the respiratory tract. Also used for the treatment of rheumatism, colds, inflammation, and bleeding wounds. It stimulates bronchial mucous gland secretion.

Adulterants: White Senega, Indian Senega and *Polygala tenuifolia.*

CYANOGENETIC GLYCOSIDES

Cyanogenic glycosides are a group of mainly plant-derived materials, which liberate hydrocyanic acid (HCN) on hydrolysis, and are thus of concern as natural toxicants. The group is identified by **amygdalin,** a constituent in the kernels of bitter almonds (*Prunus amygdalus*; Rosaceae) and other *Prunus* species such as apricots, peaches, cherries, and plums. When plant tissue containing a cyanogenic glycoside is crushed, glycosidase enzymes, usually located in different cells are brought into contact with the glycoside and begin to hydrolyse it. Thus, amygdalin is hydrolysed sequentially by β-glucosidase-type enzymes to **prunasin** and then **mandelonitrile**. Cyanogenetic glycoside contains nitrogen, but the sugar moiety is attached to oxygen. The

enzyme emulsin found in almond, consists of two enzymes amygdalase and prunase.

The main amino acids utilized in the biosynthesis of cyanogenic glycosides are phenylalanine (e.g. prunasin, sambunigrin, and amygdalin), tyrosine (e.g. dhurrin from sorghum (*sorghumbicolor*; graminae/poaceae)), valine (e.g. linamarin from flax (*linum usitatissimum*; linaceae)), isoleucine (e.g. from flax), and leucine (e.g. heterodendrin from *acacia* species (leguminosae/fabaceae)).

Chemical Test

Sodium picrate test: A strip of filter paper is dipped in 10% aqueous solution of picric acid. It is drained and redipped in 10% sodium carbonate solution and drained again. To powdered drug in a flask, water is added to moisten it. Sodium picrate is kept on the mouth of the flask. Hydrocyanic acid vapours turn the paper brick red or maroon colored.

Biosynthesis: Through shikimic acid and phenylalanine pathway.

BITTER ALMOND

Biological source: Bitter almond is dried ripe seeds of *Prunus amygdalis* var amara belonging to family rosaceae.

Habitat: The almond tree is a native of the warmer parts of western Asia and of North Africa, but it has been extensively distributed over the warm temperate region of the Old World, and is cultivated in all the countries bordering on the Mediterranean.

Botany:

- Kingdom: Plantae
- Family: Rosaceae
- Genus: Prunus
- Species: *Amygdalis*

Part used: Seeds

Chemical constituents: The bitter almond seed also contains a ferment emulsin, which in presence of water acts on the soluble glucoside amygdalin yielding glucose, prussic acid and

Fig. 9.49: Bitter almond

the essential oil of bitter almonds, or benzaldehyde, which is not used in medicine. Bitter almonds yield from 6 to 8 per cent of prussic acid. About 5 lb. of the seeds yield on the average half an ounce of the essential oil (Fig. 9.50).

Uses: This essential volatile oil of bitter almonds, under the name of 'Almond flavouring' and 'Spirit of Almonds,' is used in confectionery and as a culinary flavouring, but on account of its poisonous nature, great care ought to be exercised in its use. Bitter almonds and their poisonous properties used in intermittent fevers and as a vermifuge, and as an aperient and diuretic, and as a cure for hydrophobia. Simple water, strongly impregnated by distillation with the volatile

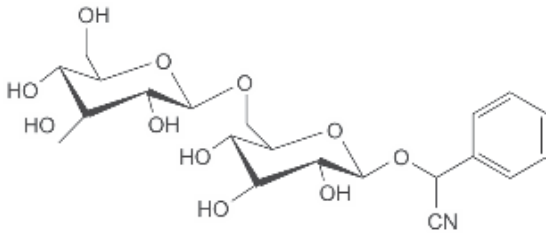


Fig. 9.50: Amygdalin

oil, will cause giddiness, headache and dimness of sight, and has been found also poisonous to animals, and there are instances of cordial spirits flavoured by them being poisonous to man.

WILD CHERRY BARK

Synonyms: **English:** Virginian Prune, Black Cherry.

Biological source: It is obtained from dried bark of *Prunus serotina* belonging to family Rosaceae.

Habitat: North America generally, especially in northern and central states.

Botany:

- Kingdom: Plantae
- Family: Rosaceae
- Genus: *Prunus*
- Species: *Serotina*

Parts used: Bark of root, trunk and branches.

Organoleptic characters: This tree grows from 50 to 80 feet high, and 2 to 4 feet in diameter. The bark is black and rough and separates naturally from the trunk.

Leaves deciduous, 3 to 5 inches long, about 2 inches wide, on petioles which have two pairs of reddish glands, they are obovate, acuminate, with incurved short teeth, thickish and smooth and glossy on upper surface.

Flowers bloom in May, and are white, in erect long terminal racemes, with occasional solitary flowers in the axils of the leaves.

Fig. 9.51: Wild cherry bark

Fruit about the size of a pea, purply-black, globular drupe, edible with bitterish taste, is ripe in August and September.

Root-bark must be freshly collected each season as its properties deteriorate greatly if kept longer than a year. It has a short friable fracture and in commerce it is found in varying lengths and widths 1 to 8 inches, slightly curved, outer bark removed, a reddish-fawn color. These fragments easily powder. It has the odor of almonds, which almost disappears on drying, but is renewed by maceration. Its taste is aromatic, prussic, and bitter. It imparts its virtues to water or alcohol, boiling impairs its medicinal properties.

Chemical constituents: Starch, resin, tannin, gallic acid, fatty matter, lignin, red coloring matter, salts of calcium, potassium, and iron, also a volatile oil associated with hydrocyanic acid by distillation of water from the bark. It also contains prunasin (a cyanogenic glycoside), emulsin, eudesmic acid, p-coumaric acid, scopoletin, tannins, sugars, etc. (Fig. 9.52).

Uses: Astringent tonic, pectoral, sedative. It has been used in the treatment of bronchitis of various types. It is valuable in catarrh, consumption nervous cough, whooping-cough, and dyspepsia.

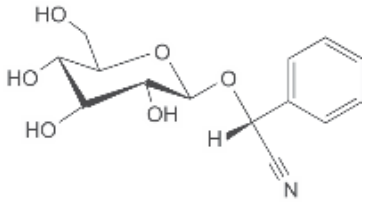


Fig. 9.52: Prunasin

FLAVANOID GLYCOSIDES

Flavanoid glycosides are mostly occurring as o-glycosides or c-glycosides containing in the cell sap of higher plants belonging to the families like compositeae, leguminoseae, rutaceae and umbelliferae.

Different types of flavanoids glycosides are:

1. Flavone glycosides, e.g. apiin and diosmin
2. Flavonol glycosides, e.g. rutin and quercetin

3. Flavanone glycosides, e.g. hesperidin and liquiritin
4. Chalcone glycosides, e.g. carthamin
5. Isoflavanoid glycosides, e.g. tephrosin and prunetrin
6. Anthrocyanidin glycosides, e.g. cyanidin and malvidin

Flavonoids are particularly beneficial, acting as antioxidants and giving protection against cardiovascular disease, certain forms of cancer, and, it is claimed, age-related degeneration of cell components. Their polyphenolic nature enables them to scavenge injurious free radicals such as superoxide and hydroxyl radicals. **Quercetin** is almost present in substantial amounts in plant tissues, and is a powerful antioxidant, chelating metals, scavenging free radicals, and preventing oxidation of low density lipoprotein.

Flavonoids in red wine (**quercetin, kaempferol**, and anthocyanidins) and in tea (**catechins** and catechin gallate esters) are also demonstrated to be effective antioxidants. Flavonoids contribute to plant colors, yellows from chalcones and flavonols, and reds, blues, and violets from anthocyanidins. Even the colorless materials, e.g. flavones, absorb strongly in the UV and are detectable by insects, probably aiding flower pollination.

Chalcones act as precursors for a vast range of **flavonoid** derivatives found throughout the plant kingdom. Flavanones can then give rise to many variants on this basic skeleton, e.g. **flavones, flavonols, anthocyanidins**, and **catechins**

Chemical tests:

1. It exhibits a brown fluorescence under UV light
2. It gives yellow precipitate with basic lead acetate solution.
3. It gives greenish brown precipitate with ferric chloride.
4. It produces a silver mirror with ammoniacal silver nitrate solution.

Biosynthesis: Through acetate pathway and shikimic acid pathway.

RUTIN

Synonyms: Rutoside, quercetin-3-rutinoside and sophorin.

Biological source: Rutin, also called rutoside, quercetin-3-rutinoside and sophorin, is a citrus flavonoid glycoside found in buck-wheat. Rutin is also found in the fruits and fruit rinds (especially *citrus* fruits (orange, grapefruit, lemon, lime) and berries such as mulberry and cranberries. Its name comes from the name of *Ruta graveolens*, a plant that also contains rutin. It is sometimes referred to as vitamin P.

Rutin is a yellow crystalline flavonol glycoside ($C_{27}H_{30}O_{16}$) that occurs in various plants (rue, tobacco, buckwheat, etc.). Upon hydrolysis (a chemical reaction that uses water to break down a compound), rutin yields quercetin and rutinose. Rutin is used in many countries as a vasoprotectant and is an ingredient in numerous multivitamin preparations and herbal remedies. The rutosides are naturally occurring flavonoids that have documented effects on capillary permeability and edema (swelling) and have been used for the treatment of disorders of the venous and microcirculatory systems. There is some evidence for the use of rutin for chronic venous insufficiency, edema, hemorrhoids, microangiopathy (disease of small blood vessels), varicosis and venous disorders.

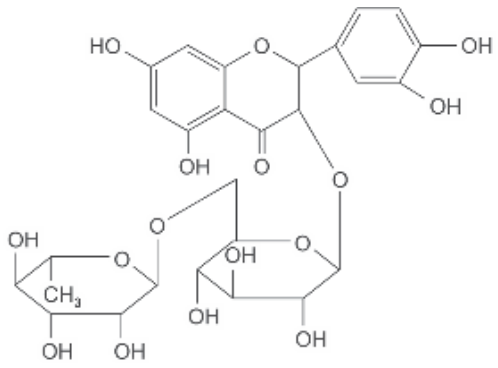


Fig. 9.53: Rutin

Uses:

- Rutin inhibits platelet aggregation, as well as capillary permeability making the blood thinner and improving circulation. Rutin has anti-inflammatory activity.
- Rutin inhibits aldose reductase activity. Aldose reductase is an enzyme normally present in the eye and elsewhere in the body. It helps change glucose (sugar-glucose) into a sugar alcohol called sorbitol.
- Rutin also strengthens the capillaries, and, therefore, can reduce the symptoms of haemophilia.
- Rutin, as ferulic acid, can reduce the cytotoxicity of oxidized LDL cholesterol and lower the risk of heart disease.
- Rutin is also an antioxidant, along with quercetin, acacetin, morin, hispidulin, hesperidin, and naringin, it was found to be the strongest. Hydroxyethylrutosides, synthetic hydroxyethyl acetylations of rutin, are used in the treatment of chronic venous insufficiency.

HESPERIDIN

Synonyms: Hesperetin 7-rhamnoglucoside, hesperetin-7-rutinoside.

Biological source: Hesperidin is a flavanone glycoside (flavonoid) ($C_{28}H_{34}O_{15}$) found abundantly in citrus fruits. Its aglycone form is called hesperetin. Hesperidin is the predominant flavonoid in lemons and oranges.

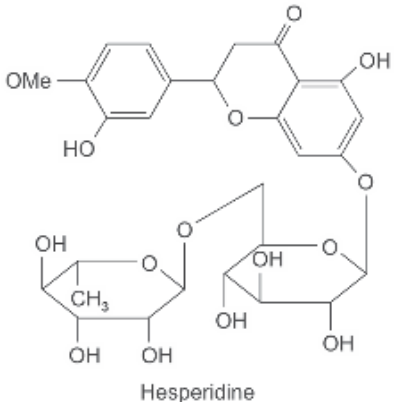


Fig. 9.54: Hesperidin

The peel and membranous parts of these fruits have the highest hesperidin concentrations. Sweet oranges (citrus sinensis) and tangelos are the richest dietary sources of hesperidin. Hesperidin is classified as a citrus bioflavonoid. Hesperidin, rutin and other flavonoids thought to reduce capillary permeability and to have anti-inflammatory action were collectively known as vitamin P.

Uses: Hesperidin has antioxidant, anti-inflammatory, hypolipidemic, vasoprotective and anticarcinogenic and cholesterol lowering actions. Hesperdin can inhibit following enzymes: Phospholipase A2, lipoxygenase, HMG-CoA reductase and cyclo-oxygenase. Hesperidin improves the health of capillaries by reducing the capillary permeability. Hesperidin is used to reduce hay fever and other allergic conditions by inhibiting the release of histamine from mast cells. The possible anti-cancer activity of hesperidin could be explained by the inhibition of polyamine synthesis.

ISOTHIOCYANATE GLYCOSIDES

Isothiocyanate glycosides contain sulphur and present in many cruciferous plants. On hydrolysis they produce isothiocyanate aglycones. Sinigrin from black mustard and sinalbin from white mustard are isothiocyanate glycosides. Sinigrin on hydrolysis in the presence of enzyme myrosin, yields allyl isothiocyanate, glucose and potassium acid sulphate. These glycosides are irritant and employed as counter irritant in neuralgia and rheumatism.

Chemical test:

1. The powdered black mustard seeds on treatment with sodium hydroxide yields bright yellow coloration.
2. The hydrolysed products of sinalbin (white mustard) are crystalline and give rise a bright yellow coloration in alkaline medium.

PHENOLIC GLYCOSIDES

Simple phenolic glycosides have their aglycone portion loaded with phenolic moieties, alcoholic moieties or carboxylic acid functions.

Commonly found phenolic glycosides are salicin, populin, arbutin, gaultherin, etc.

Biosynthesis: Through shikimic acid pathway.

Chemical tests:

1. It gives a bright yellow coloration with conc. sulphuric acid that fades out on addition of water.
2. It yields blue coloration with ferric chloride solution.

TERPENOIDS, VOLATILE OILS AND RESINS

Terpenoids

Terpenes are unique, widespread and chemically diverse groups of hydrocarbon-based natural products whose structure may be derived from combinations of several 5-carbon-base (C5) units called isoprene, giving rise to structures which may be divided into isopentane (2-methylbutane) units. The terpenes are of a biogenetic origin, in which isopentenyl pyrophosphate and dimethylallyl pyrophosphate combine to yield geranyl pyrophosphate, leading to monoterpenes. Similarly, sesquiterpenes, and triterpenes are formed from two equivalents of farnesyl pyrophosphate. A terpene containing oxygen is called a terpenoids.

Terpenes are thus classified by the number of 5-carbon units they contain:

1. Hemiterpenes C_5
2. Monoterpene C_{10}
3. Sesquiterpene C_{15}
4. Diterpene C_{20}
5. Sesterterpene C_{25} (very rare)
6. Triterpene C_{30}
7. Tetraterpenes C_{40}

The function of terpenes in plants is as follows, it is generally considered to be both ecological and physiological:

- It inhibits the growth of competing plants (allelopathy).
- It shows insecticidal activity as well as found to attract insect pollinators.
- The plant hormone, abscissic acid, is one of the sesquiterpenes.
- Gibberellic acid is a type of terpene, and is major plant hormones.

Table 9.8: Types of terpenes

The monoterpenes are formed from the coupling of two isoprene units (c10). They are the most representative molecules constituting 90% of the essential oils and allow a great variety of structures. They consist of several functions:

1.	Carbures	Acyclic: Myrcene, ocimene, etc. Monocyclic: Terpinenes, p-cimene, phellandrenes, etc. Bicyclic: Pinenes, -3-carene, camphene, sabinene, etc.
2.	Alcohols	Acyclic: Geraniol, linalol, citronellol, lavandulol, nerol, etc. Monocyclic: Menthol, α-terpineol, carveol bicyclic: Borneol, fenchol, chrysanthenol, thuyan-3-ol, etc.
3.	Aldehydes	Acyclic: Geranial, neral, citronellal, etc.
4.	Ketone	Acyclic: Tegetone, etc. Monocyclic: Menthones, carvone, pulegone, piperitone, etc. Bicyclic: Camphor, fenchone, thuyone, ombellulone, pinocamphone, pinocarvone, etc.
5.	Esters	Acyclic: Linalyl acetate or propionate, citronellyl acetate, etc. Monocyclic: Menthyl or α-terpinyl acetate, etc. Bicyclic: Isobornyl acetate, etc.
6.	Ethers	1,8-cineole, menthofurane, etc. Peroxydes: Ascaridole, etc.
7.	Phenols	Thymol, carvacrol, etc.

Examples of plants containing monoterpenoids are (+)-α-pinene from *Pinus palustris*, (–)-β-pinene from *Pinus caribaea*, (–)linalol from coriander, (+)-linalol from some camphor trees, (±)-citronellol is widespread, the form (+) is characteristic of *Eucalyptus citriodora*.

The sesquiterpenes are formed from the assembly of three isoprene units (c15). The extension of the chain increases the number of cyclisations which allows a great variety of structures. The structure and function of the sesquiterpenes are similar to those of the monoterpenes:

1.	Carbures	Azulene, β-bisabolene, cadinenes, β-caryophyllene, logifolene, curcumenes, elemenes, farnesenes, zingiberene, etc.
2.	Alcohols	Bisabol, cedrol, β-nerolidol, farnesol, carotol, β-santalol, patchoulol, viridiflorol, etc.
3.	Ketones	Germacrone, nootkatone, cis-longipinan-2,7-dione, β-vetivone, turmerones, etc.
4.	Epoxide	Caryophyllene oxide, humulene epoxides, etc.

Examples of plants containing these compounds are angelica, bergamot, caraway, celery, citronella, coriander, eucalyptus, geranium, juniper, lavandin, lavander, lemon, lemongrass, mandarin, mint, orange, peppermint, petitgrain, pine, rosemary, sage, thyme.

Aromatic compounds are derived from phenylpropane, the aromatic compounds occur less frequently than the terpenes.

1.	Aldehyde	Cinnamaldehyde
2.	Alcohol	Cinnamic alcohol
3.	Phenols	Chavicol, eugenol
4.	Methoxy derivatives	Anethole, elemicine, estragole, methyleugenols
5.	Methylene dioxy compounds	Apiole, myristicine, safrole

The principal plant sources for these compounds are anise, cinnamon, clove, fennel, nutmeg, parsley, sassafras, star anise, tarragon, and some botanical families (apiaceae, lamiaceae, myrtaceae, rutaceae).

Volatile Oils

Volatile oils are volatile, natural, complex compounds characterized by a strong odor and are formed by aromatic plants as secondary metabolites. They can be synthesized by all plant organs, i.e. buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood or bark, and are stored in secretory cells, cavities, canals, epidermic cells or glandular trichomes. They are liquid, volatile, limpid and rarely colored, lipid soluble and soluble in organic solvents with a generally lower density than that of water. They are usually obtained by steam or hydro-distillation, known for their antiseptic, i.e. bactericidal, virucidal and fungicidal, and medicinal properties and their fragrance, they are used in embalment, preservation of foods and as antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic and locally anesthetic remedies. Due to their bactericidal and fungicidal properties, pharmaceutical and food uses are more and more widespread as alternatives to synthetic chemical products to protect the ecological equilibrium. Volatile oils are very complex natural mixtures which can contain about 20–60 components at quite different concentrations, also known as essential oils.

Table 9.9: Plant essential oil with chemical constituents

S. No.	Plant essential oil	Chemical constituents
1.	*Origanum compactum*	Carvacrol (30%) and thymol (27%)
2.	*Coriandrum sativum*	Linalol (68%)
3.	*Artemisia herba-alba*	α- and β-thuyone (57%) and camphor (24%)
4.	*Cinnamomum camphora*	1, 8-cineole (50%)
5.	*Anethum graveolens* (Leaf)	α-Phellandrene (36%) and limonene (31%)
6.	*Anethum graveolens* (Seed)	Carvone (58%) and limonene (37%)
7.	*Mentha piperita*	Menthol (59%) and menthone (19%)

Physical Properties of Volatile Oil

- Volatile essential oils are volatile and become liquid at room temperature.
- When distilled they are at first colorless or slightly yellowish.
- They are soluble in alcohol and in the usual organic solvents, such as ether or chloroform.
- They are less dense than water (sassafras essence and clove essence being exceptions).
- They are nearly always rotational and have a high refractory index.
- They are lipo-soluble and not very soluble in water, but can be dragged using steam.

Classifying Essential Oils

Essential oils may be classified using different criteria: Consistency, origin, and chemical nature of the main components.

a. Consistency

Depending on their consistency, essential oils are classified as: Essences, balsams, resins.

1. Fluid **essences** are liquids which are volatile at room temperature.
2. **Balsams** are natural extracts obtained from a bush or tree. They usually have a high benzoic and cynamic acid content with their corresponding esthers. They are thicker, not very volatile, and less likely to react by polymerising. Examples of balsams are copaiba balsam, peruvian balsam, banguy balsam, tolu balsam, liquid amber.

   Within the resin group we find a number of possible combinations and mixes:
3. i. **Resins.** These are amorphous solid or semi-solid products of a complex chemical nature. They are physiological or physiopathological in origin. Colophony, for example, is obtained by separating trementine an oleoresin. It contains abietic acid and derivates.

   ii. **Oleoresins.** The term oleoresin is also used to refer to vegetable extracts obtained using solvents, which should be virtually free of said solvents. They are frequently used instead of spices in foodstuffs and pharmacy because of their advantages (stability, microbiotic and chemical uniformity, and easy to add). They have the aroma of the plant in concentrated form and are highly viscous liquids or semi-solid substances. These are homogeneous mixes of resins and essential oils. Trementine, for example, is obtained by making incisions in the trunk of different pine species. It contains resin (colophony) and essential oil (trementine essence) which are separated by steam drag distillation.

   Example: Black pepper, paprika oleoresin, cloves.

   iii. **Gum-resins.** These are natural plant or tree extracts. They are a mix of gums and resins.

b. Origin

Depending on their origin, essential oils are classified as: Natural, artificial, synthetic.

Natural oils are obtained straight from the plant and are not modified physically or chemically afterwards. However, they are expensive because of their limited yield.

Artificial oils are obtained using processes of enriching the essence with one or several of its components. For example, essences of rose, geranium, and jasmine are enriched with linalool, and aniseed essence with athenol. Synthetic oils, as the name suggests, are usually produced by combining their chemically synthesised components. These are the cheapest and are thus much more commonly used as fragrance and taste enhancers (vanilla, lemon and strawberry essences).

c. Chemical Nature

The total essential oil content of a plant is generally low (less than 1%). However, by extraction, we obtain a highly concentrated form which is used in industrial processes. Most of these are highly complex chemical compounds. The proportion of these substances varies depending on the oil, but also

on season, time of day, growing conditions, and genetics.

The term **chemotype** refers to the variation in chemical composition of an essential oil, even of the same species. A chemotype is a distinct chemical entity, different from secondary metabolites. Certain small variations in the environment, geographical location, genes which have a little or no effect on a morphological level can, however, produce big changes in chemical phenotypes. Thyme (*Thymus vulgaris*) is a typical example. It has 6 different chemotypes depending on which is the main component of its essence (timol, carvacrol, linalool, geraniol, tuyanol-4, or terpineol). When this is the case, the plant is named using the name of the species followed by the main component of its chemotype. For example, *Thymus vulgaris* linalool, *Thymus vulgaris* timol.

Extraction

There are several methods for extracting essential oils. These may include use of liquid carbon dioxide or microwaves, and mainly low or high pressure distillation employing boiling water or hot steam. The chemical profile of the essential oil products differs not only in the number of molecules but also in the stereochemical types of molecules extracted, according to the type of extraction, and the type of extraction is chosen according to the purpose of the use. The extraction product can vary in quality, quantity and in composition according to climate, soil composition, plant organ, age and vegetative cycle stage. So, in order to obtain essential oils of constant composition, they have to be extracted under the same conditions from the same organ of the plant which has been

Table 9.10: Classification of terpenoids

Classification (suffix)	Functional group	Important constituents	Examples	Properties
Terpenoids hydrocarbons (-ene)	–C=C–	Cadinene, camphene, pinene, lemonene	Turpentine, junipes, cade	Stimulant, antiviral, antitumoral
Alcohol (-OH)	C–OH	Linalol, menthol, santalol, geraniol	Coriander, peppermint, sandalwood	Antimicrobial, antiseptic, spasmodic
Aldehyde (-al)	CHO	Cinnamaldehyde, citral, citonellal	Cinnamon, clove, lemon peel	Spasmodic, sedative, antiviral
Esters (-ate)		Linalyl acetate, bornyl acetate	Ceaultheria, lavender, rosemary	Spasmodic, antifungal, sedative
Ketones (-one)		Carvone, camphor, menthone	Caraway, dill, camphor	Mucolitic, neurotoxic, regenator cellular
Ethers	–C–O–C–	Chavical methyl ether cineol, mepisticin, ascaridol	Arise, eucalyptus, nutmeg	Expectorant and stimulant
Peroxides	–O–O–	Ascaridole	Chenopodium	Insect repellant. Increase digestion
Phenol (-ol)	Ar-OH	Eugenol, thymol, carvacrol	Clove, cinnamon leaf, thyme	Antimicrobial, stimulant, irritant
Phenolic ether	Ring-O-C	Safrol, anetol, miristicine	Sassafras, anise seed	Flavouring agent, carminative, expectorant
Glycoside derived	Sugar and non-sugar group	Methyl salicylate allyl isothiocynate benzaldehyde	Wintergreen, mustard, bitter almond	Flavouring agent

growing on the same soil, under the same climate and has been picked in the same season. There are four ways of extraction of volatile oils:

1. Expression
2. Steam distillation
3. Extraction by volatile solvents
4. Adsorption in purified fat (Effleurage)

1. Expression

The plant material is crushed and the juice is screened to remove the large particles.The rind is lacerated, and the contents of the ruptured secretory cavities are recovered.

Classic process: An abrasive action is applied on the surface of the fruit in a flow of water. The solid waste is eliminated, and the essential oil separated from the aqueous phase by centrifugation.

Other process: Machines break the cavities by depression, and collect the essential oil directly. It prevents the degradation linked to the action of water.

The screened juice is centrifuged at a high speed when nearly half of the essential oils is extracted. The other half of the oil is generally not extracted and such residue is used for isolation of the inferior quality of oil by distillation.

Example: Citrus, lemon and grass oils.

2. Steam Distillation

i. ***Simple steam distillation:*** This is most widely used method, the plant material is macerated and then steam distilled. Heterogeneous vapours are condensed on a cold surface. Essential oil separates based on difference in density and immiscibility. However the method should be used with a great care, since some essential oils are decomposed during distillation and some (esters) are hydrolysed to non or less fragment compounds.

ii. ***Saturated steam:*** When plant does not come into contact with the water, steam is injected through the plant material placed on perforated trays. It is possible to operate under moderate pressure.
Advantages: Limits the alteration of the constituents of the oil, it shortens the duration of the treatment, it conserves energy and it can also be conducted on on-line in automated set ups.

iii. ***Hydrodiffusion:*** In this method pulses of steam is sent through the plant material at very low pressure from top to bottom.
Advantage: Normally produces a product of high quality and it saves time as well as energy.

iv. ***Steam distillation by microwaves under vacuum:*** In this procedure, the fresh plant (require no water) is heated selectively by microwave radiation in a chamber inside which the pressure is reduced sequentially.
Advantage: This method is fast, consumes a little energy and yields a product which is most often of a higher quality than the traditional steam distillation product.

3. Extraction by means of Volatile Solvents

Some volatile essential oils are sensitive to heat and hence decomposed during distillation, in such cases the plant material is directly treated with light petrol at 50°C and the solvent is then removed by distillation under reduced pressure.

4. Enfluerage

The fat taken in glass plates is warmed to about 50°C, then its surface is covered with the petals and it is allowed to be kept as such for several days until the fat is saturated with the essential oils for which the old petals may be replaced by the fresh ones. The petals are then removed and the fat is digested with ethyl alcohol when the essential oils present in fat are dissolved in ethyl alcohol. And if some fat is also dissolved during digestion it is removed by cooling to about 20°C. The extract having ethyl alcohol and essential oils is distilled under reduced pressure to remove the solvent. But recently the activated coconut

charcoal is used in place of fat owing to the greater stability and more surface as compared to fat.

5. Extraction by Supercritical Gases

For perfume uses, extraction with lipophilic solvents and sometimes with supercritical extraction is favored because beyond its critical point, a fluid can have the density of a liquid and the viscosity of a gas therefore diffuses well through solids, resulting in a good solvent. CO_2 is the main gas used due to its advantages that are chemically inert, non-flammable, non-toxic, selective, inexpensive, readily available and easy to completely eliminate.

Disadvantage: Technical constraints and high cost of initial investment.

Advantages: Itobtains extracts which are very close in composition to the natural product and it is possible to adjust the selectivity and viscosity, etc by fine tuning the temperature and pressure.

Example: Ginger, paprika, celery (spice extracts), black tea, oak wood smoke.

Separation

Chemical methods:

1. Volatile oil treated with NaCl in chloroform. The product are separated and decomposed and collected.
2. Terpenoid alcohol volatile oil is separated with reaction with pthalic anhydride to form diesters.
3. Terpenoid aldehyde and ketone are separated by reaction with carbonyl reagent, $NaHCO_3$ and 2–4 drops of di-nitrophenyl hydrazine and Grignard reagent through which are isolated terpenoids, ketones and aldehydes.

Physical distillation:

1. Fractional distillation
2. Chromatography

1. Fractional distillation: During such type of distillation mono terpenoid hydrocarbon and try oxygenated derivatives and residue contain sesquiterpenes which are unextracted.

2. Chromatography: Adsorption chromatography is generally used by using silica gel and alumina used as isolation technique. Most of the commercialized essential oils are chemotyped by gas chromatography and mass spectrometry analysis.

Identification Tests of Volatile Oils

1. Volatile oil treated with Sudan red-III reagent produces red color.
2. Volatile oil treated with tincture of alkana shows red color.
3. Volatile oil treated with cosmic acid does not show stain.
4. Volatile oil at filter paper does not show stain.

NUTMEG

Synonyms: Sanskrit: Jati palam, English: Nutmeg, Bengali: Jayiphal, Telugu: Jajikaya.

Biological source: It is obtained from dried kernel of seeds of *Myristica fragrans* belonging to family: Myristicaceae.

Habitat: Banda Islands, Malayan Archipelago, Molucca Islands, and cultivated in Sumatra, French Guiana.

Botany:

- Kingdom: Plantae
- Order: Magnoliales
- Family: Myristicaceae
- Genus: *Myristica*
- Species: *Fragrans*

Part used: Dried kernel of the seed.

Organoleptic Characters

Color: Externally: Greenish brown

Odor: Strongly aromatic

Taste: Pungent and aromatic

Shape: Ellipsoidal

Size: 20 to 30 mm in length, 20 mm broad (Fig. 9.55).

Chemical constituents: They contain lignin, stearin, volatile oil, starch, gum and 0.08 of an acid substance. By submitting nutmegs and water to distillation, a volatile oil is obtained. The small round heavy nutmeg is the best. The powder of nutmegs, beaten to a pulp with water, then pressed between heated plates, gives from 10 to 30 per cent of orange colored scented concrete oil erroneously called 'oil of mace'.

Chemical test:

- Thin section of drug is treated with Sudan red III solution, red colored globules are seen under microscope.
- Thin section of drug is treated with a few drops of tincture, alkana red color is seen.

Uses: Powdered nutmeg is rarely given alone, though it enters into the composition of a number of medicines. The expressed oil is sometimes used externally as a gentle stimulant. It is used as a local stimulant to the gastrointestinal tract.

Adulterants: Bombay nutmeg, papua nutmeg.

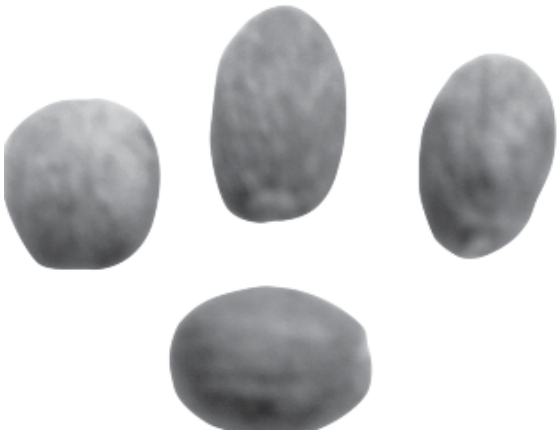


Fig. 9.55: Nutmeg

CARDAMOM FRUITS AND SEEDS

Synonyms: Sanskrit: Ela, Truti, Kapita, English: Cardamom, Bengali: Chota Elachi, Hindi: Chhoti Elachi.

Biological source: It is obtained from dried ripe seeds and fruits of *Elettaria cardamomum* belonging to Family: Zingiberaceae

Habitat: Southern India.

Botany:

- Kingdom: Plantae
- Order: Zingiberales
- Family: Zingiberaceae
- Genus: *Elettaria*
- Species: *Cardamomum*

Parts used: Dried ripe seeds, oil from fruits.

Table 9.11: Organoleptic characters of cardamom

Macroscopic characters	Cardamom seeds	Cardamom Fruits
Color	Dark reddish brown	Pale buff
Odor	Characteristic	Characteristic
Taste	Strongly aromatic	Strongly aromatic
Shape	Irregularly angular	Ovoid and oblong
Size	Up to 4 mm	1 to 2 cm long

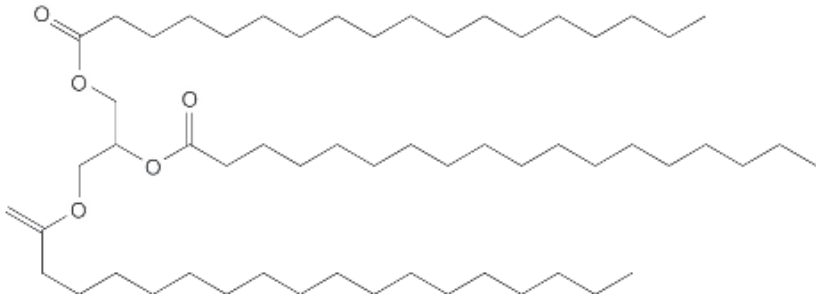


Fig. 9.56: Stearin

Fig. 9.57: Cardamom fruits and seeds

Extra features: **Seeds:** The seeds consist of Periderm: Large and it contains starch, Endosperm: Small translucent contains aleurone grains and Embryo: Small and contain aleurone grain.

Fruits: Fruits consist of apex which is beaked and rounded base with stalk.

Chemical constituents: The seeds contain volatile oil, fixed oil, salt of potassium, a coloring principle, starch, nitrogenous mucilage, ligneous fiber, an acrid resin, and ash. The volatile oil contains terpenes, terpineol and cineol. It is colorless when fresh, but becomes thicker, more yellow, and less aromatic. It is very soluble in alcohol and readily soluble in four volumes of 70 per cent alcohol, forming a clear solution.

Chemical test:

- Thin section of drug is treated with sudan red III solution, red colored globules are seen under microscope.
- Thin section of drug is treated with a few drops of tincture alkana, red color is seen.

Standards:

- **Acid value:** 1 to 4
- **Ester value:** 90 to 150
- **Refractive index:** 1.4620 to 1.4675
- **Specific gravity:** 0.923 to 0.945
- **Optical rotation:** 24° to 48°

Uses: Carminative, stimulant, aromatic, but rarely used alone; chiefly useful as an adjuvant or corrective. The seeds are helpful in indigestion and flatulence, giving a grateful but not fiery warmth. When chewed singly in the mouth the flavour is not unpleasant, and they are said to be good for colic and disorders of the head.

Adulterants: Long wild native cardamom, korarima cardamom.

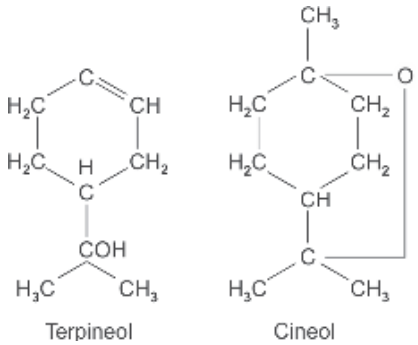


Fig. 9.58: Chemical constituents of cardamom

DILL

Synonyms: **Sanskrit**: Misroya, Sthatapusphi, **English**: Dill, Dill seed **Hindi**: Sowa, **Punjabi**: Soya, **Tamil**: Shatakupivirai.

Biological source: It consists of dried ripe fruits of *Peucedanum graveolens* Family: NO compositae.

Habitat: Dill is a hardy annual, a native of the Mediterranean region and Southern Russia. It grows wild among the corn in Spain and Portugal and upon the coast of Italy, but rarely occurs as a cornfield weed in Northern Europe.

Fig. 9.59: Dill

Botany:

- Kingdom: Plantae
- Order: Apiales
- Family: Umbelliferae
- Genus: *Peucedanum*
- Species: *Graveolens*

Part used: Dried ripe fruit.

Organoleptic characters

- **Color:** Chocolate brown
- **Odor:** Aromatic and spicy
- **Taste:** Aromatic and spicy

Extra features: Dorsally compressed, mericarps are separated.

Microscopy of Dill Fruit (Fig. 9.60)

Epicarp: The epicarp composed of a layer of colorless cells with uniform, well-marked cuticular striations.

Vittae: The brown fragments of the vittae, which are composed of thin-walled polygonal cells.

Mesocarp: The sclereids of the mesocarp occur in groups composed of fairly thick-walled cells, square to rectangular. The occasional groups of reticulate parenchyma of the mesocarp composed of elongated cells with fairly thick, lignified walls traversed by numerous conspicuous, rounded to oval pits. The innermost layer of the mesocarp composed of yellowish-brown cells with thick walls which are usually lignified and have few, indistinct pits.

Endocarp: The endocarp composed of a layer of thin-walled, lignified cells which are elongated and arranged in groups with the long axes of the adjacent groups approximately parallel to one another.

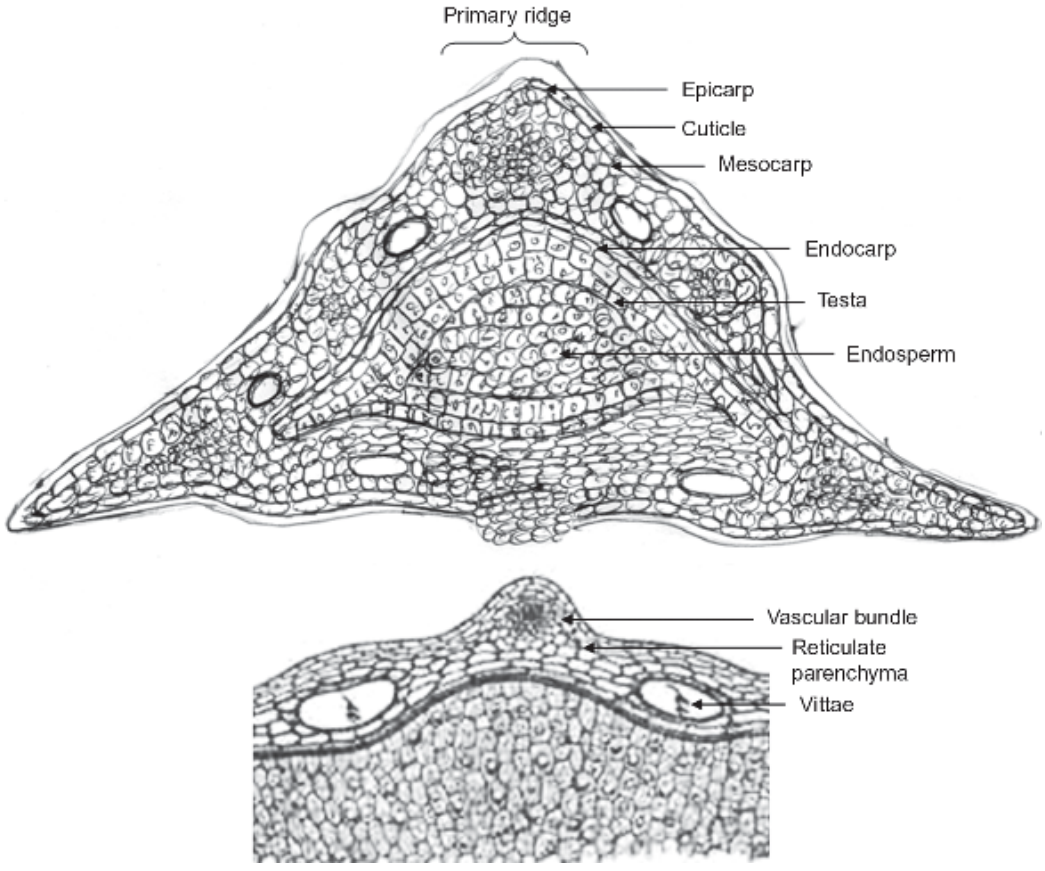


Fig. 9.60: Transverse section (TS) of dill plant

Testa: The testa, composed of a single layer of small, brown, thin-walled cells, polygonal.

Endosperm: The abundant endosperm composed of thick-walled cells containing aleurone grains and microrosette crystals of calcium oxalate.

Fibro-vascular bundle: The fragments of lignified fibro-vascular tissue composed of small groups of fibres and vessels showing spiral and annular thickening.

Chemical constituents: The fruit yields about 3.5 per cent of the oil, which is a mixture of a paraffin hydrocarbon and 40 to 60 per cent of d-carvone, with d-limonene.

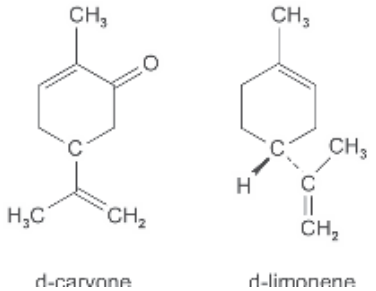


Fig. 9.61: Chemical constituents of dill plant

Staining Reagents

Phloroglucinol: HCl-1:1 (lignified tissues are seen red/pink).

Alcholic picric acid: Aleurone grain (yellow).

Sudan red III: Cutin/cuticle (pink).

Chemical Test

Test for volatile oil: Soluble in 90% alcohol, filter paper is not permanently stained.

Uses: Dill possesses stimulant, aromatic, carminative and stomachic properties, making them of considerable medicinal value.

Substitutes: Indian dill (*anethum sowa*, umbelliferae).

Cumin fruits (*cuminum cyminum*, umbelliferae).

FENNEL

Synonyms: **Sanskrit:** Madhurika, Methica **English:** Indian sweet fennel **Hindi:** Badi or Bari Saunf, **Bengali:** Panmouri, Methi.

Biological source: It consists of dried ripe fruits of *Foeniculum vulgare*, it contains NLT 1.4% of volatile oil, family Umbelliferae.

Habitat: It grows wild in most parts of temperate Europe, but is generally considered indigenous to the shores of the Mediterranean, whence it spreads eastwards to India.

Botany:

- Kingdom: Plantae
- Order: Apiales
- Family: Apiaceae
- Genus: *Foeniculum*
- Species: *F. vulgare*

Parts used: Seeds, leaves and roots.

Organoleptic Characters

Color: Greenish or yellowish brown.

Odor: Sweet, aromatic and characteristic.

Taste: Sweet, mucilaginous, aromatic and characteristic.

Extra features: Fennel exhibits cremocarp. It consists of equal portions called mericarps, connected by central stalks called carpophore.

Fig. 9.62: Fennel

Microscopy of Fennel (Fig. 9.63)

Epicarp: The epicarp composed of a layer of colorless, thin-walled cells, polygonal in surface view with a smooth cuticle. Stomata are found on some of the fragments but generally are not numerous.

Mesocarp: The innermost layer of the mesocarp, which is composed of slightly thick-walled cells, rounded to rectangular.

Vittae: The numerous brown fragments of the vittae composed of thin-walled cells, polygonal in surface view.

Reticulate parenchyma: The reticulate parenchyma of the mesocarp composed of ovoid or elongated, subrectangular cells. The walls are thickened and lignified and have conspicuous oval or rounded pits.

Endocarp: The endocarp composed of a layer of thin-walled, lignified cells, elongated and arranged in groups of about six or more cells with their long axes parallel to one another.

Endosperm: The abundant endosperm composed of moderately thick-walled cells containing aleurone grains and microrosette crystals of calcium oxalate.

Fibro-vascular tissue: The fragments of lignified fibro-vascular tissue composed of small fibres, vessels and tracheids, and occasional larger vessels with reticulate thickening.

Staining Reagents

Phloroglucinol: HCl-1:1 (lignified tissues are seen red/pink).

Alcoholic picric acid: Aleurone grain (yellow) Sudan red III—cutin/cuticle are seen pink.

Chemical constituents: Volatile oil (4 to 6%), anethol (50 to 60% of volatile oil), d-fenchone (10% of volatile oil), fixed oil (12 to 18%), proteins (14 to 22%).

Chemical test: **Test for volatile oil:** Soluble in 90% alcohol, filter paper is not permanently stained.

Uses: Carminative, respiratory stimulant.

Adulterants: Exhausted fruit.

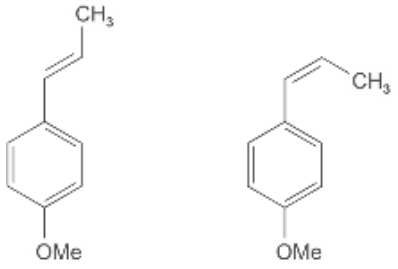


Fig. 9.64: Anethol

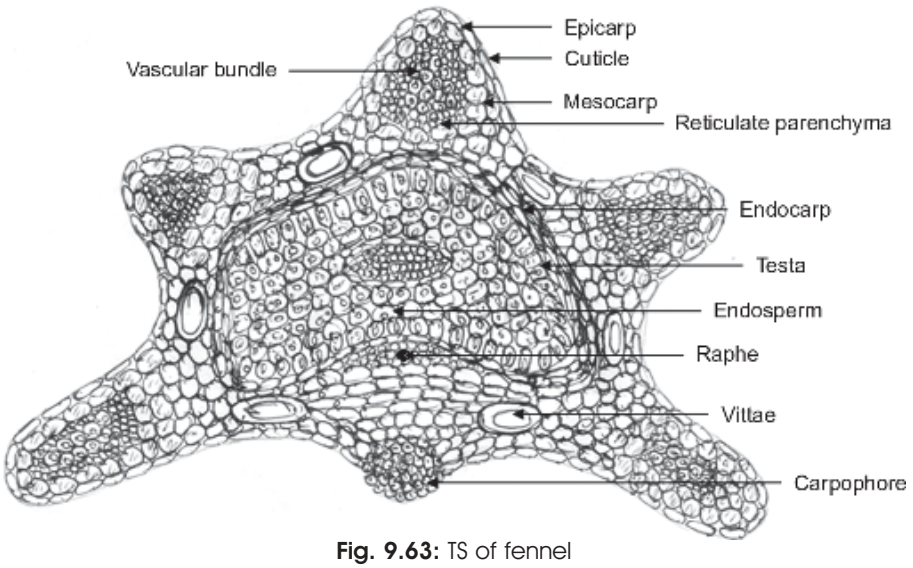


Fig. 9.63: TS of fennel

CARAWAY

Synonyms: **Sanskrit:** Ajaji, Jeeraka, **English:** Cumin seed, caraway seed, **Hindi:** Safed jeera, zira, **Gujarati**: Safed jiraun.

Botany:

- Kingdom: Plantae
- Order: Apiales
- Family: Apiaceae
- Genus: *Carum*
- Species: *C. carvi*

Part used: Fruit.

Fig. 9.65: Caraway

Organoleptic Characters

Color: Brown.

Odor: Characteristic and aromatic.

Taste: Hot, spicy and characteristic.

Microscopy of Caraway (Fig.9.66)

Epicarp: The epicarp composed of colorless cells with a striated cuticle, stomata are fairly numerous and are parallel to those of the cells of the epicarp.

Vittae: The brown fragments of vittae composed of thin-walled polygonal cells.

Mesocarp: The sclereids of the mesocarp are usually in a single layer with unlignified, thin-walled parenchymatous cells.

Endocarp: This layer is usually found adherent to fragments of the testa. The endocarp composed of large cells with thin, slightly lignified walls. They appear rounded or radially elongated.

Testa: It is composed of a single layer of brown, thin-walled cells, polygonal, which is adherent to the endocarp.

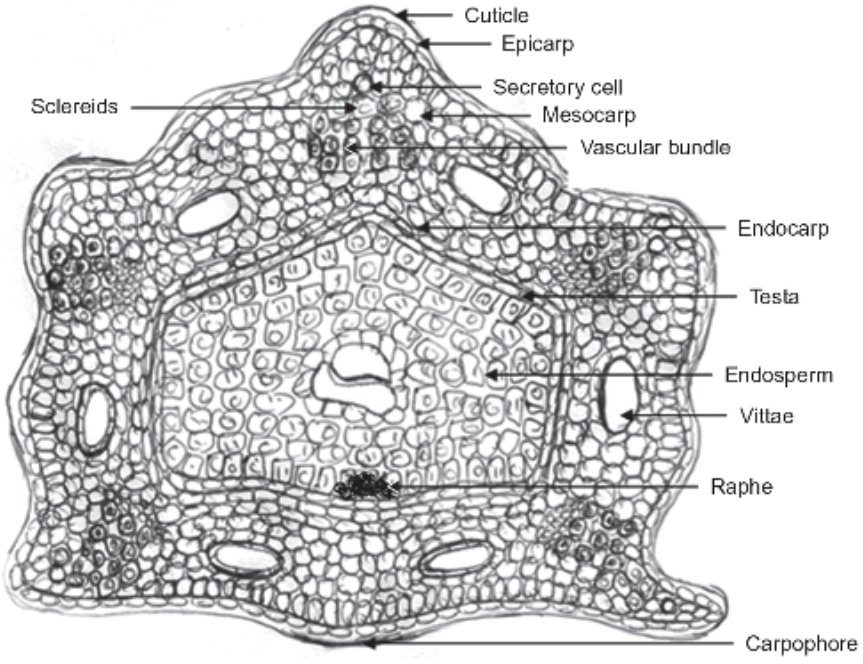


Fig. 9.66: TS of caraway

Endosperm: The abundant endosperm containing aleurone grains and microrosette crystals of calcium oxalate.

Staining Reagents

Phloroglucinol: HCl—1:1 (lignified tissues are seen red/pink).

Alcholic picric acid: Aleurone grain (yellow).

Sudan red III—cuticle are seen pink.

Chemical constituents: It consists of volatile oil: Carvone, carveol, dihydrocarvone, limonene, protein, fat, fiber, carbohydrates, calcium, phosphorous, sodium, potassium, vitamin B_1, B_2, C, A.

Uses: Both fruit and oil possess aromatic, stimulant and carminative properties.

Adulterants: Exhausted fruit, caraway stalks, cummin fruits.

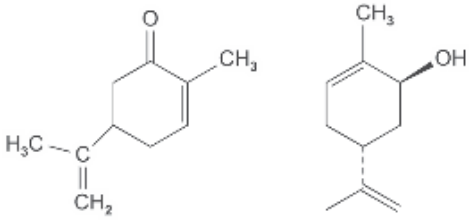


Fig. 9.67: Chemical constituents of caraway

CORIANDER FRUIT

Synonyms: **Sanskrit:** Kustumbari, Dhanyaka **English:** Coriander **Hindi:** Kottmir, Dhania, **Bengali:** Dhane.

Biological source: It consists of dried ripe fruits of *Coriandrum sativum* belonging to family umbelliferae. It should contain NLT 0.3% of volatile oil.

Habitat: Coriander, an umbelliferous plant indigenous to southern Europe, is found occasionally in Britain in fields and waste places, and by the sides of rivers. It is frequently found in a semi-wild state in the east of England.

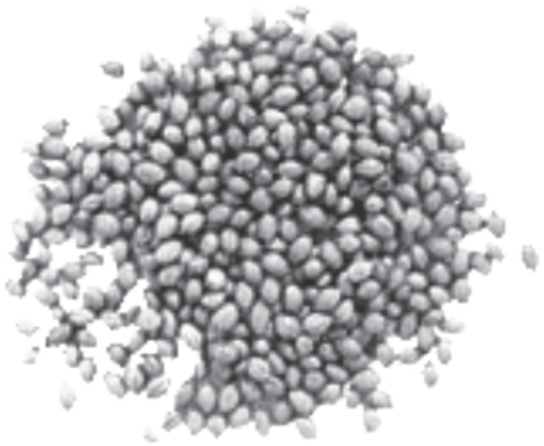


Fig. 9.68: Coriander

Botany:

- Kingdom: Plantae
- Order: Apiales
- Family: Apiaceae
- Genus: *Coriandrum*
- Species: *C. sativum*

Parts used: Fruits and leaves.

Organoleptic Characters

Color: Brownish yellow

Odor: Aromatic

Taste: Spicy and characteristic

Extra features: The fruits (so-called seeds) are of globular form, beaked, finely ribbed, 1/5 inch in diameter, with five longitudinal ridges, separable into two halves (the mericarps), each of which is concave internally and shows two broad, longitudinal oil cells (vittae). The seeds have an aromatic taste and, when crushed, a characteristic odor.

Microscopy of Coriander (Fig. 9.69)

Epicarp: It is composed of a layer of polygonal, colorless, thin-walled cells, with a smooth cuticle. Most of the cells contain small prisms of calcium oxalate.

Mesocarp: The sclerenchyma of the mesocarp consist of two types of cells masses of very thick-walled, sinuous, fusiform cells with a

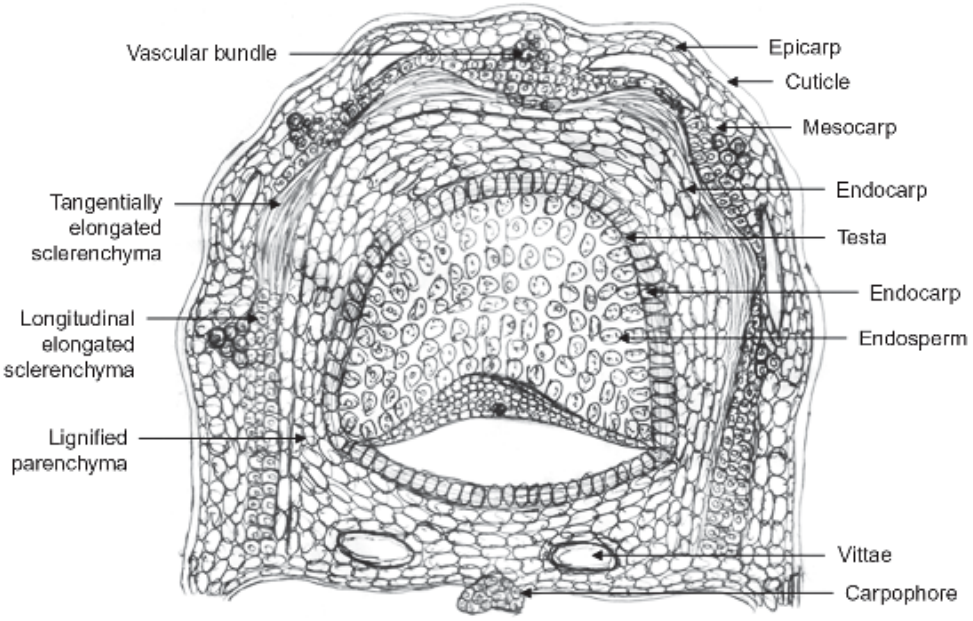


Fig. 9.69: TS of coriander

narrow lumen and two or three layers of large, rectangular or polygonal cells with only slightly thickened walls.

Endocarp: The endocarp composed of a layer of thin-walled, lignified cells, elongated. It is usually found adherent to the rectangular sclereids of the mesocarp.

Vittae: The brown fragments of the vittae composed of thin-walled cells, polygonal.

Testa: It is a single layer of brown, very thin-walled polygonal cells.

Endosperm: The endosperm is composed of thick-walled cells containing microrosette crystals of calcium oxalate and aleurone grains.

Staining Reagents

Phloroglucinol: HCl—1:1 (lignified tissues are seen red/pink).

Alcholic picric acid: Aleurone grain (yellow). Sudan red III—cuticle are seen pink.

Chemical constituents: Coriander fruit contains about 1% of volatile oil. It also contains coriandrol (d-linalool–60–70%), terpenes (20%), fixed oil (13 to 20%) and proteins (17%). The fruit yields about 5 per cent of ash and contains also malic acid, tannin and some fatty matter.

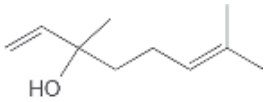


Fig. 9.70: d-Linalool

Uses: Stimulant, aromatic and carminative.

Adulterants: Bombay coriander (less volatile oil, bigger and ellipsoidal in shape).

CINNAMON BARK

Synonyms: **Sanskrit:** Gudatvak, Varangam, **English:** Cinnamon, **Telugu and Tamil:** Lowangapatta, **Bombay:** Dalchini, Taj.

Biological source: It consists of dried bark of *Cinnamomum zeylanicum,* belonging to family lauraceae.

Habitat: Ceylon, but grows plentifully in Malabar, Cochin-China, Sumatra and Eastern Islands. It has also been cultivated in the Brazil, Mauritius, India, Jamaica, etc.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Laurales
- Family: Lauraceae
- Genus: *Cinnamomum*
- Species: *C. verum*

Part used: Bark

Organoleptic Characters

Color: Outer surface—dull yellowish brown. Inner surface—darker in color.

Odor: Fragrant.

Taste: Warm, sweet and aromatic.

Extra features: Fracture—splintery.

Microscopy of Cinnamon Bark (Fig. 9.71)

Cork: The very occasional fragments of cork.

Sclereids: It occurs singly or in small groups but are usually more or less isodiametric, the walls of most of the cells are moderately thickened and occasional cells have very thick walls with a small lumen and striations are visible.

Fibres: The fibres are single, thick-walled and lignified with a small, uneven lumen. Some fibres are found with the sclereids of the pericycle, oil cells and parenchyma of the phloem.

Starch granules: The starch granules are small, simple or compound with up to four or more components are found scattered in the parenchymatous tissues and in the sclereids. Hilum (rounded or slit-shaped) is visible in some of the larger granules.

Oil cells: The thin-walled oil cells, frequently found associated with the parenchyma or fibres of the phloem; the cells are large, ovoid, and usually occur singly.

Parenchyma: The thin-walled parenchyma and medullary rays of the phloem contains numerous small, acicular crystals of calcium oxalate.

Staining Reagents

Phloroglucinol: HCl—1:1 (lignified tissues are seen red/pink).

Iodine solution: Starch (blue).

Ruthenium red: Pink (mucilage cells).

Tincture of alkana: Volatile oil (red on standing).

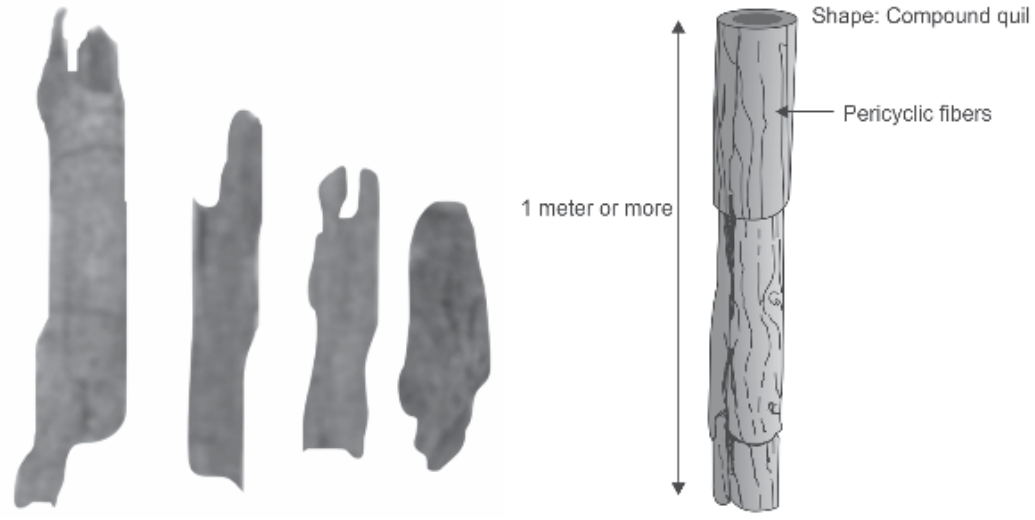


Fig. 9.71: Cinnamon bark

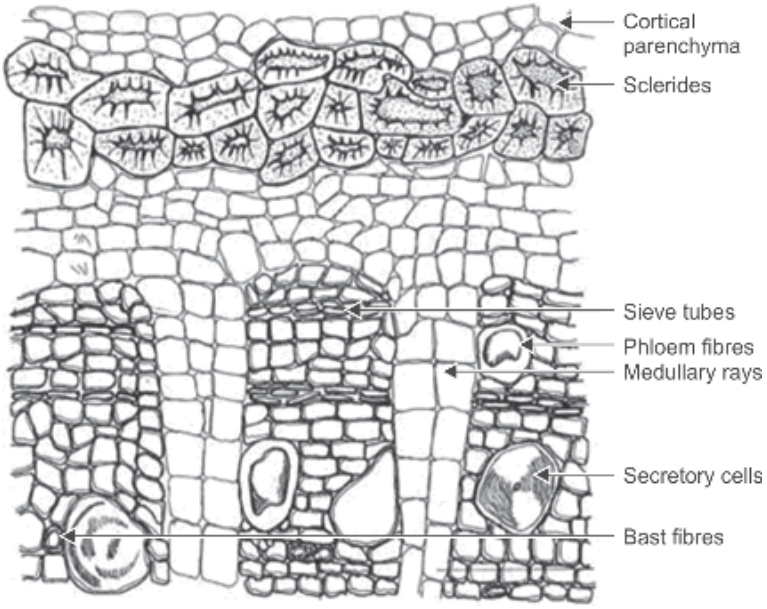


Fig. 9.72: TS of cinnamon

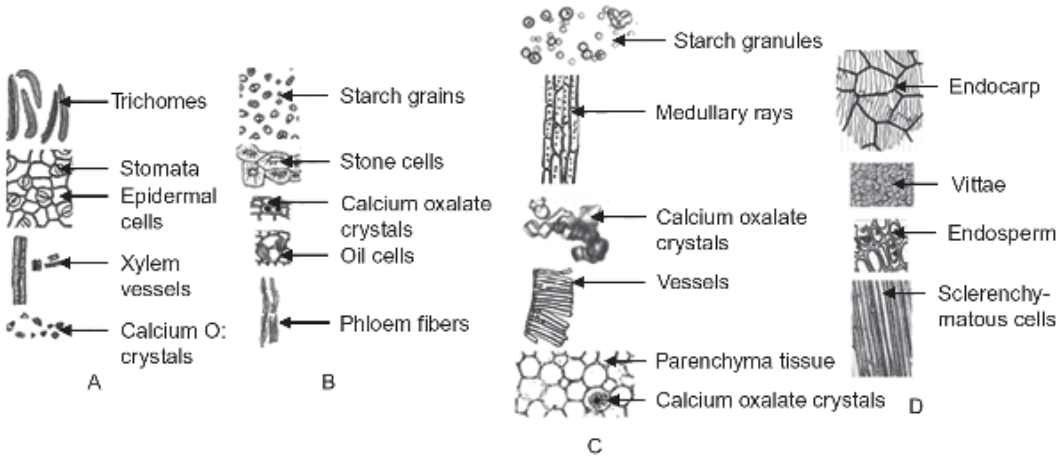


Fig. 9.73: Microscopy of powdered cinnamon

Chemical Constituents: 0 to 10 % of volatile oil, cinnamic aldehyde (55 to 65%), eugenol (4 to 10%), terpenes, mucilage, starch, calcium oxalate, tannin, mucilage and sugar.

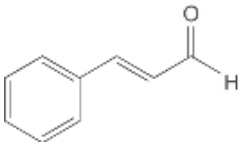


Fig. 9.74: Cinnamic aldehyde

Chemical Test

***Test for volatile oil*:** Chloroform extract of volatile oil on slide treated with 10% aqueous phenyl hydrazine hydrochloride solution rod-shaped crystals of cinnamic aldehyde are seen.

Test for tannins: Aqueous extract treated with ferric chloride dark color indicate presence of tannins.

Uses: Carminative, astringent, stimulant, antiseptic; more powerful as a local than as a general stimulant; is prescribed in powder and infusion but usually combined with other medicines. It stops vomiting, relieves flatulence, and given with chalk and astringents is useful for diarrhoea and haemorrhage of the womb.

Adulterants: Cassia bark, Chinese cinnamon.

CLOVE

Synonyms: **Sanskrit:** Gudatvak, Varangam, **English:** Cinnamon, **Telugu and Tamil:** Lowangapatta, **Bombay:** Dalchini, Taj.

Biological source: It consists of dried flower buds of *Eugenia caryophyllata* belonging to family Myrtaceae. It contains NLT 15% v/w of clove oil.

Habitat: Molucca Islands, Southern Philippines.

Botany:

- Kingdom: Plantae
- Order: Myrtales
- Family: Myrtaceae
- Genus: *Syzygium*
- Species: *S. aromaticum*

Part used: Undeveloped flowers.

Organoleptic Characters

Color: Dark brown or crimson color.

Odor: Aromatic

Taste: Spicy

Microscopy of Clove (Fig. 9.76)

Epidermis: The epidermis is composed of small, polygonal cells with slightly thickened walls; large, almost circular anomocytic stomata, the underlying tissue contains very large, brown, ovoid oil glands and occasional cluster crystals of calcium oxalate.

Parenchyma: The very abundant yellowish-brown parenchyma of the hypanthium in which the oil glands are embedded; the cells are frequently unevenly thickened and appear collenchymatous; they contain numerous small cluster crystals of calcium oxalate.

Calcium oxalate: The cluster crystals of calcium oxalate in the parenchymatous tissue but are rarely found scattered; they vary in size and are usually composed of a large number of small, sharply pointed components.

Fibres: The occasional fibres, which are found singly or in groups of two or three cells; they are rather short and broad with bluntly pointed ends. The walls are lignified, usually strongly thickened.

Anther: The fragments of the fibrous layer of the anther composed of rather small cells; in sectional view the lignified thickening on the side walls of the cells appears as closely packed longitudinal bands and these are seen as small beads in surface view.

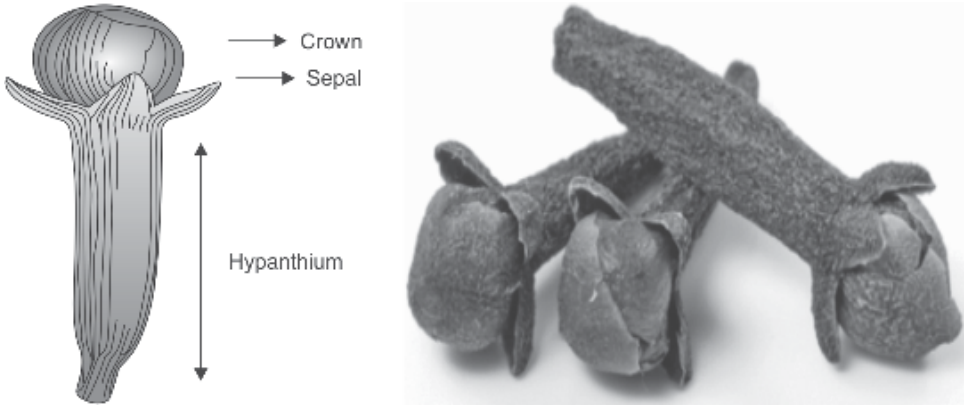


Fig. 9.75: Clove bud

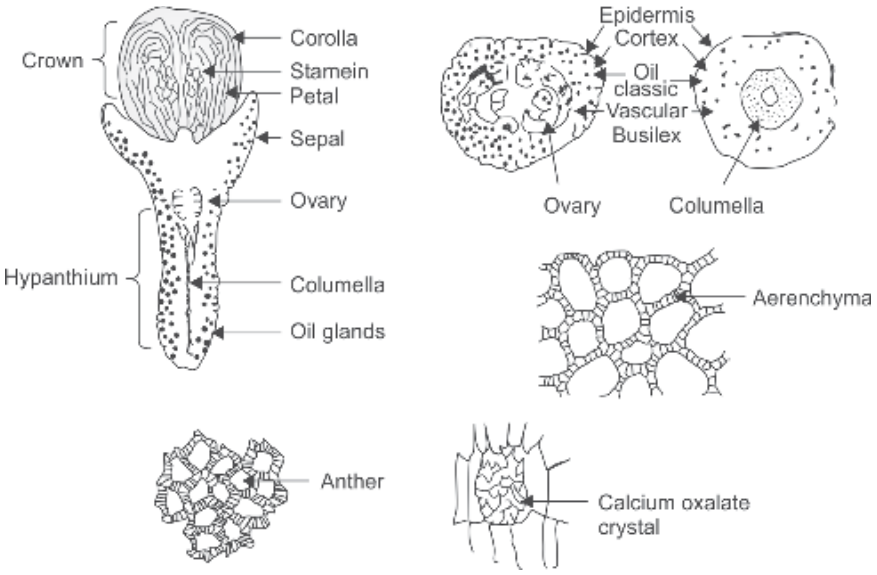


Fig. 9.76: TS of clove bud

Pollen grains: The abundant pollen grains which are small, biconvex with a rounded, triangular outline. A number of immature pollen grains also occur and these may be found in closely packed masses, frequently enclosed in the pollen sacs.

Aerenchyma: The occasional fragments of the aerenchyma of the hypanthium composed of chains of two or three parenchymatous cells with moderately thickened walls; the contiguous walls of adjacent cells are traversed by numerous very small pits.

Sclereids: The very occasional sclereids from the stalk; they are oval to subrectangular in outline with strongly thickened and striated walls which have numerous simple or branched pits; the lumen is frequently filled with brown contents.

Staining Reagents

Phloroglucinol: HCl—1:1 (lignified tissues are seen red/pink).

Sudan red III: Cuticle are seen pink.

Strong KOH needle-shaped potassium eugenate crystals (eugenol).

Chemical constituents: Volatile oil, gallotannic acid, two crystalline principles caryophyllin,

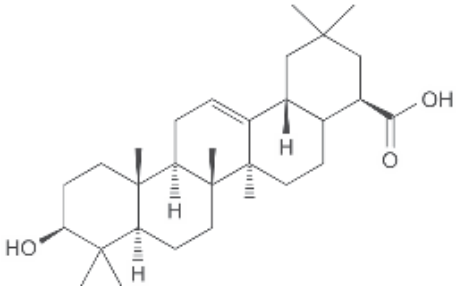


Fig. 9.77: Caryophyllin

which is odorless and appears to be a phylosterol, eugenin, gum, resin, fibre.

Chemical Test

Test for eugenol: Clove oil treated with alcohol and ferric chloride (5%) gives blue coloration.

Test for tannins: Aqueous extract treated with lead acetate solution gives white precipitate.

Uses: Stimulating and carminative given in powder or infusion for nausea emesis, flatulence, languid indigestion and dyspepsia.

Adulterants: Exhausted cloves, mother cloves and clove stalks.

GINGER

Synonyms: Hindi—Sonth, English—Zingiber, rhizome zingiberis, Jamica ginger.

Biological source: It consists of rhizome of *Zingiber officinalis* roscoe, family Zingiberaceae. Scrapped to remove outer skin and dried in the sun.

Habitat: Native to Southeast Asia, cultivated mainly in Kerala, Andhra Pradesh, Uttar Pradesh, West Bengal, Maharashtra.

Botany:

- **Kingdom:** Plantae
- **Division:** Angiosperma
- **Class:** Monocotyledoneae
- **Order:** Scitaminaea
- **Family:** Zingiberaceae
- **Genus:** *Zingiber*
- **Species:** *Officinale*

Organoleptic Characters (Fig. 9.78)

Color: Externally buff colored.

Odor: Agreeable and aromatic.

Taste: Agreeble, pungent and characteristic.

Size: 3 to 6 cm.

Shape: Irregular.

Fracture: Short and fibrous.

Extra features: Sympodial branching, horizontal rhizome, transversely cut surface shows well-marked endodermis and stele.

Fig. 9.78: Ginger

Chemical constituents: Ginger contains usually 1–3% of volatile oil, pungent principles viz., gingerols and shogaols and about 6–8 lipids and others. Ginger oil contains zingiberene and bisaboline as major constituents along with other sesqui and monoterpenes. Ginger oleoresin contains mainly the pungent principles gingerols and shogaols as well as zingiberone. Shogaols have recently been found to be twice as pungent as gingerols.

Standards:

- Foreign matter: NMT 1.0%
- Total ash: NMT 8.0%
- Acid insoluble ash: NMT 1.0%
- Moisture content: NLT 12.0%
- Alcohol soluble extractive: NLT 7.0%
- Water soluble extractive: NLT 14.0%
- Petroleum ether extractive: 1.5–2.5%
- Chloroform extractive: 3–5%
- Methanol extractive: 2–4%

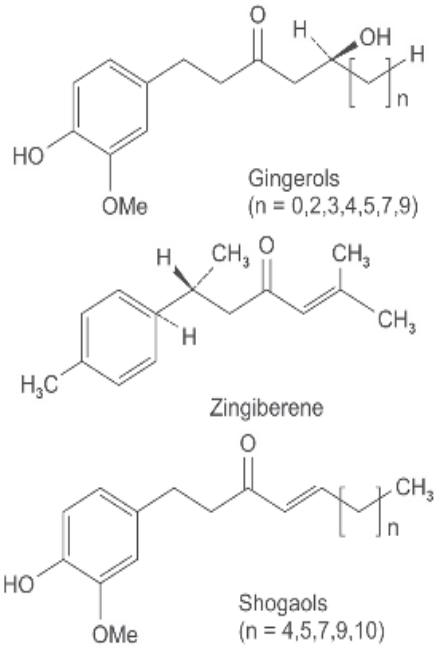


Fig. 9.79: Chemical constituents of ginger

Microscopy of the Rhizome (Fig. 9.80)

Outer and inner cork: Few layers with irregularly arranged parenchymatous cells. The

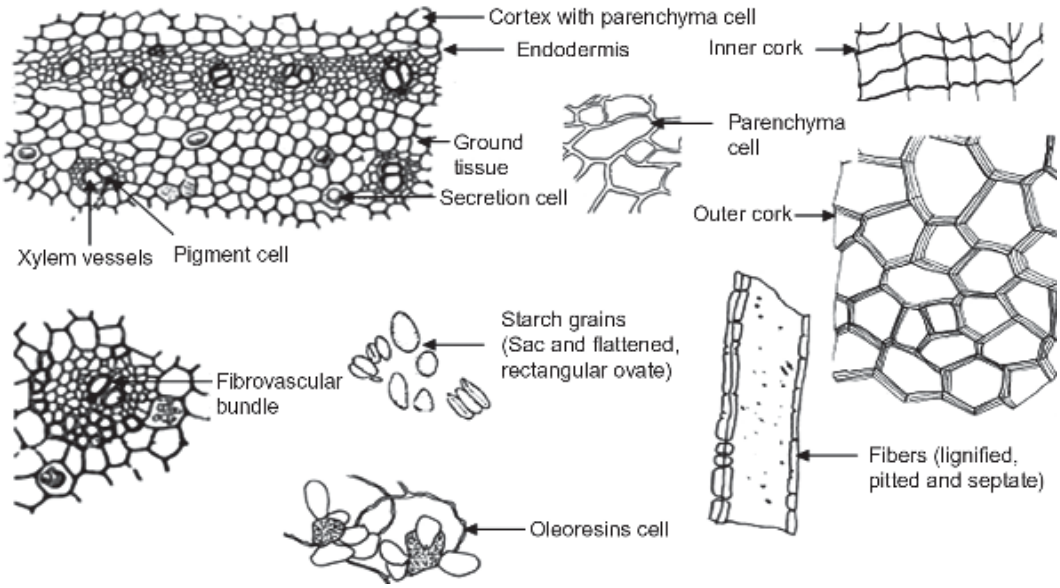


Fig. 9.80: Microscopic features of ginger rhizome

outer cork cells are dark colored brown, whereas inner cells are colorless.

Cortex with parenchymatous cells: The cortex is isodiametric with thin-walled parenchymatous cells.

Fibrovascular bundles: Collateral, conjoint and closed in nature.

Xylem vessels: The xylem vessel gives no reaction for lignin and they have reticulate or spiral thickening, and are often accompanied by narrow, thin-walled cells containing dark brown pigment; a few smaller, spirally or annularly thickened vessels also occur.

Fibres: Lignified, pitted and septate.

Starch: Starch abundant in the thin-walled ground tissue, as flattened, ovate to sub-rectangular, transversely striated, simple granules, each with the hilum in a projection towards one end.

Oleoresin cells: Bright yellow to reddish brown ovoid to spherical cells occurring in small groups in the parenchyma or singly.

Pigment and secretion cells: Pigments cells with dark reddish brown contents occurring either singly in the ground tissue or in axial rows accompanying the vascular bundles.

Sclereids and calcium oxalate crystals absent.

Chemical test: The drug is boiled with 50% KOH or alkali its pungency is destroyed.

Uses: Ginger is carminative, pungent, stimulant, used widely for indigestion, stomachache, malaria and fevers. It is used for abdominal pain, anorexia, arthritis, atonic dyspepsia, bleeding, cancer, chest congestion, chickenpox, cholera, chronic bronchitis, cold extremities, colic, colitis, common cold, cough, cystic fibrosis, diarrhoea, difficulty in breathing, dropsy, fever, flatulent, indigestion, disorders of gallbladder, hyperacidity, hypercholesterolemia, hyperglycemia, indigestion, morning sickness, nausea, rheumatism, sore throat, throat ache, stomach ache and vomiting.

Adulterants: Spent or exhausted ginger, wormy ginger, unscraped ginger and capsicum powder.

TURMERIC (Fig. 9.81)

Synonyms: Curcuma, turmeric, ukon, goeratji, kakoenji, koenjet, kondin, kunir, kunyit,

Fig. 9.81: Turmeric

oendre, rame, renet, temu kuning, temu kunyit, tius.

Biological source: It is obtained from rhizome of *Curcuma longa*, family Zingiberaceae.

Habitat: Cultivated extensively in India within tropical climate.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Liliopsida
- Order: Zingiberales
- Family: Zingiberaceae
- Genus: *Curcuma*
- Species: *C. longa*

Organoleptic Characters

Color: Yellowish brown

Odor: Characteristics

Taste: Slightly bitter

Shape: Oblong

Fracture: Horny

Extra features: Root scars and annulations are present.

Chemical constituents: The active constituents of turmeric are the flavonoid curcumin and volatile oils including tumerone, atlantone, and zingiberone. Other constituents include sugars, proteins, and resins. The active constituent is curcumin, which comprises 0.3 to 5.4 percent of raw turmeric. It also consists of 1, 8-cineole, 2-bornanol, 2-hydroxy-methyl-anthraquinone, 4-hydroxy-cinnamoyl-(Feruloyl)-methane, curcumene, curcumenol, curcumin, curdione, curlone and curzerenone.

Microscopy of Turmeric Rhizome

Cork cells: The outer most surface consists of cork cells.

Parenchyma cells: Parenchyma cells are filled with gelatinised starch and yellow coloring matter.

Epidermis: Epidermis are present on surface, it shows the presence of stoma and cicatrix.

Covering trichomes: This is type of trichomes present in turmeric.

Starch granules are also present.

Vessels: Spirally and reticulately thickened vessels.

Chemical test:

- Turmeric powder with sulphuric acid gives crimson color.
- Turmeric powder is treated with acetic anhydride and concentrated sulphuric acid, it gives violet color (visible), red fluorescence (UV).

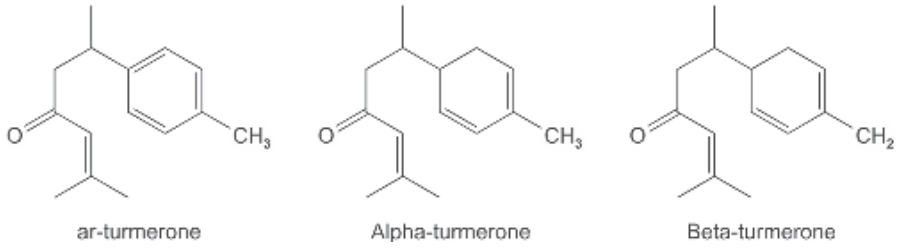


Fig. 9.82: Chemical constituents of turmeric

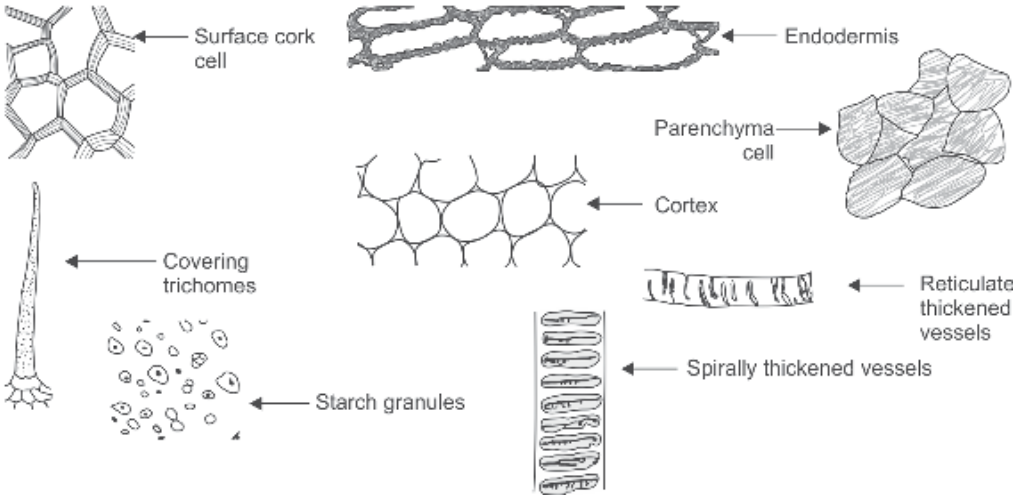


Fig. 9.83: Microscopic features of turmeric rhizome

- Aqueous solution of turmeric powder with boric acid gives reddish brown color which turns to greenish blue on addition of alkali.

Uses: Anti-inflammatory, antioxidant, anti-mutagenic, anti-cancerous, cholagogueue, depurative, diuretic, fumitory, hemostatic, hepatoprotective, lactagogue, stomachic, tonic, vulnerary.

Substituents: *C. aromatica*, *C. amada*, *C. zeodaria*, *C. xanthorrhiza.*

Adulterants: Metanil yellow coloring.

When concentrated hydrochloric acid is added to a solution of turmeric powder, it turns magenta if metanil yellow is present.

TANNINS

Tannins are astringent, bitter plant polyphenols that either bind and precipitate or shrink proteins and various other organic compounds including amino acids and alkaloids. Tannins are distributed in species throughout the plant kingdom. They are commonly found in both gymnosperms as well as angiosperms. Botanically, tannins are mainly physically located in the vacuoles or surface wax of plants. These storage sites keep tannins active against plant predators, Tannins are found in leaf, bud, seed, root, and stem tissues.

There are three major classes of tannins:

1. Hydrolyzable tannins
2. Non-hydrolyzable tannins or condensed tannins
3. Pseudotannins

Hydrolyzable Tannin

Hydrolyzable tannins are mixtures of poly-galloyl glucoses and/or poly-galloyl quinic acid derivatives containing in between 3 up to 12 gallic acid residues per molecule. Hydrolyzable tannins are hydrolyzed by weak acids or weak bases to produce carbohydrate and phenolic acids. They are tannins on heating with hydrochloric or sulphuric acids yield gallic or ellagic acids. While hydrolyzable tannins and most condensed tannins are water soluble. Examples of gallotannins are the gallic acid esters of glucose in tannic acid ($C_{76}H_{52}O_{46}$), found in the leaves and bark of many plant species.

Non-hydrolyzable or Condensed Tannin

Condensed tannins, also known as proanthocyanidins, are polymers of 2 to 50 (or more) flavonoid units that are joined by carbon-carbon bonds, which are not susceptible to

being cleaved by hydrolysis. They on heating with hydrochloric acid yield phlobaphenes like phloroglucinol. Some very large condensed tannins are insoluble.

Condensed tannins from *lithocarpus glaber* leaves have been analysed through acid-catalyzed degradation in the presence of cysteamine and have a potent free radical scavenging activity.

Pseudo Tannins

Pseudo tannins are low molecular weight compounds associated with other compounds. They do not answer gold beater skin test unlike hydrolysable and condensed tannins.

Properties of Tannins

Hydrolysable tannins are yellow-brown amorphous substances which dissolve in hot water to form colloidal dispersions. They are astringent and have the ability to tan hide. Chemically speaking, they are esters which can be hydrolyzed by boiling with dilute acid to yield a phenolic compound, usually a derivative of gallic acid, and a sugar. These are often referred to as pyrogallol tannins.

Condensed tannins are polymers of phenolic compounds related to the flavonoids and are similar in general properties to the hydrolysed tannins but are not very soluble in water and following treatment with boiling dilute acid red-brown insoluble polymers known as phlabaphenes or tannins-red are formed.

Chemical Test of Tannins

Gelatin-block test: This test employs aqueous extract prepared from 80% ethanol extracted plant material. A sodium chloride solution is added to one portion of the test extract, of 1% gelatine solution to a second portion, and the gelatine salt reagent to a third portion. Precipitation with the latter reagent or with both the gelatine and gelatine-salt reagents is indicative of the presence of tannins. If precipition is observed only with the salt solution a false-positive test is indicated. Positive test are confirmed by the addition of ferric chloride solution to the extract and should result in a blue, blue-black, green or blue-green color and precipitate.

Gambier fluorescein test: The powdered drug is boiled with alcohol and filtered and to the filtrate solution of NaOH is added stirred and few ml of light petroleum is added. The petroleum layer shows green fluorescence.

Extraction of Tannins

The process used to extract tannins is the hydrosolubilization. Because this process operates with temperatures around 100°C, the extraction process motives a hydrocracking of sugar and other organic compounds with a darkening of the final product. The supercritical extraction process as alternative procedure to obtain the natural raw material to leather tannage. In which supercritical carbon dioxide and polar or non-polar co-solvents were used as solvents.

The advantages of supercritical extraction process with regard to hydrosolubilization and solvent extraction are low extraction temperature, short extraction time and absence organic solvent concentration in the extract.

ARJUNA BARK

Synonyms: **Sanskrit**–Arjuna, **English**–Arjuna Myrobalan, **Hindi**–Arjun, Kahu, **Gujarati**–Sajadan.

Biological source: Arjuna is dried bark of *Terminalia arjuna*, family Combretaceae.

Origin: *Terminalia arjuna* is common throughout India especially in the sub-himalayan tracts and Eastern India.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Myrtales
- Family: Combretaceae

Fig. 9.84: Arjuna bark

- Genus: *Terminalia*
- Species: *Arjuna*

Organoleptic Characters

Color: Externally it is pink or flesh colored with mealy coating and internal surface is reddish brown.

Odor: None

Taste: Gritty and astringent

Fracture: Fibrous

Size: Varying size with 5 to 10 mm thickness

Extra features: 40 meter high deciduous tree. Leaves are simple, 4–6″ long oppositely arranged, rectangular or oval. At the base of the lamina two glands are present. Flower: Green and star-like spikes, calyx smooth. Fruit: Truncate.

Chemical constituents: The bark contains specific medicinal active constituents, namely triterpene glycosides like arjenetosides I, II, III, IV, arjunine and arjunetin. It is also rich in saponins, natural antioxidants (flavonoids-arjunone, arjunolone, leteilin) gallic acid, ellagic acid, oligomeric proanthocyanidins, phytosterols, rich in minerals like calcium, magnesium, zinc and copper.

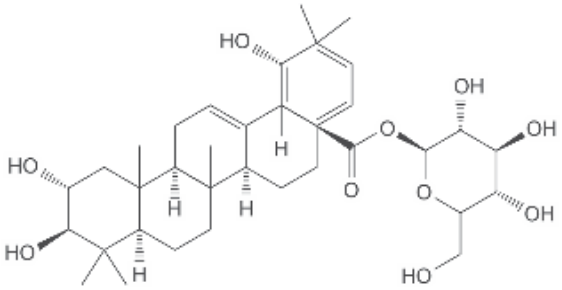


Fig. 9.85: Arjunetin

Chemical Test

Fluorescence analysis: The fluorescence analysis is carried out with 10% extract of ether and petroleum ether in UV chamber.

Table 9.12: Comparative chemical test

Chemicals	*T. arjuna*	*T. tomentosa*
Ether	Pinkish white	Pale blue
Petroleum ether	Bright pinkish red	Pale white blue

Uses: The bark is astringent, sweet, acrid, cooling, aphrodisiac, cardiotonic, urinary astringent, expectorant, alexiteric and is useful in fractures, ulcers, cirrhosis of the lever, hyperhidrosis, otalgia and hypertension.

Adulterants: *Terminalia tomentosa* (dried bark). It is distinguish by Arjuna bark by fluorescence test.

ASHOKA BARK

Synonyms: **Sanskrit:** Ashoka, **English:** Ashoka tree, **Gujarati:** Asupala, **Telugu:** Asok.

Biological source: Ashoka is dried bark of *Saraca indica* family leguminosae.

Habitat: India, abundantly found in central and eastern himalayas and extending up to burma.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Fabales
- Family: Fabaceae/leguminosae
- Genus: *Saraca*
- Species: *Indica*

Fig. 9.86: Ashoka bark

Organoleptic Characters

Color: Outer surface: Rough, rusty brown in color, inner surface: Smooth, reddish brown in color.

Odor: Indistinct.

Taste: Astringent.

Size: 40 cm in length, 3–6 cm wide, and 5–8 mm thick.

Fracture: Short and fibrous.

Chemical constituents: It contains condensed tannins, catechol, sterol, ketosterol and organic calcium compound.

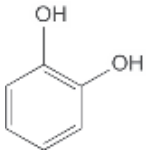


Fig. 9.87: Catechol

Chemical test:

1. With ferric chloride they show green color.
2. With bromine water it gives ppt.
3. With vanillin: Alcohol: Dil HCl (1:10:10) it gives red color.

Uses: Menorrhagia (scant menses), dysmenorrhea (painful menses, menstrual cramps), depression, bleeding hemorrhoids, uterine fibroids, considered a uterine sedative and tonic.

Adulterants: Bark of *polyalthia longifolia* (anonaceae).

AMLA

Synonyms: **Sanskrit: Dhatri-pala, English:** Indian Gooseberry, Emblic myrobalan, **Hindi:** Amla, Amlika.

Biological source: It consists of fruits of *Emblica officinalis,* belonging to family euphorbiaceae.

Origin: It is found throughout India till the height of 4500 feet.

Botany:

- Kingdom: Plantae
- Division: Flowering plant
- Class: Magnoliopsida
- Order: Malpighiales
- Family: Phyllanthaceae
- Tribe: Phyllantheae
- Subtribe: Flueggeinae
- Genus: *Phyllanthus*
- Species: *Emblica*

Parts used: Fresh fruit, dried fruit, the nut or seed, leaves, root, bark and flowers. Ripe fruits used generally fresh, dry also used.

Organoleptic Characters

Color: Green when unripe and light yellow when mature.

Odor: None.

Fig. 9.88: Amla fruit

Taste: Sour, slightly bitter.

Size: 1.3–1.6 cm in diameter.

Extra features: Fruits are globose and depressed six lobed, hard and smooth in appearance.

Chemical constituents: The major chemical constituents of amla are phyllemblin, ascorbic acid (vitamin C), gallic acid, tannins, pectin, etc. It contains 81.2% moisture, 0.5% proteins, 0.1% fats, carbohydrates 14.1%, calcium 0.05%, phosphorus 0.02%, iron 1.2 mg and nicotinic acid 0.2 per 100 gm.

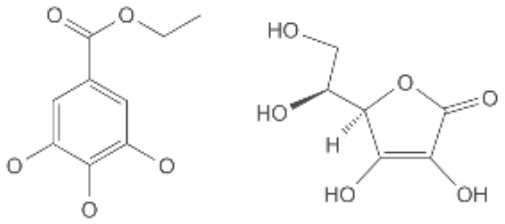


Fig. 9.89: Chemical constituents of amla fruit

Chemical test:

1. To 0.5 g of powder add 10 ml of hot water allowed to stand for 5 min shake frequently and filter. Add 1% gelatin containing 10% NaCl to 5 ml of filterate milky white color is produced.
2. To the aqueous solution of amla, add lead acetate or gelatin, remove precipitate by filtration. To the filtrate add solution of 2, 6 dicholorophenol indophenol colors disappear.

Standards:

- Foreign matter: NLT 3.0%
- Total ash: NMT 5.0%
- Acid-insoluble ash: NMT 2.0%
- Alcohol-soluble extractive: NLT 40.0%
- Water-soluble extractive: NLT 40.0%

Uses: Amla is a wonder herb with numerous indications. Due to its sheet virya potency, it is widely used in diseases caused by pitta disorders. It has found an esteemed place in ayurvedic preparations. Chawanprash, triphala and amlaki rasayan possess dominance of amla. It is used to substitute vitamin C in disease like scurvy. It has actions on all the systems of the body.

BAHERA

Synonyms: **Sans.:** Vibhitaki, **Hindi:** Bahera, Bhaira, **Ben.:** Bohera.

Biological source: It is obtained from fruits of *Terminalia belerica*, Family: Combretaceae.

Habitat: A tree common in Indian forest and plant.

Botany:

- Kingdom: Plantae
- Family: Combretaceae
- Genus*: Terminalia*
- Species: *Belerica*

Organoleptic Characters (Fig. 9.90)

Color: Grey-velvetty wooly hairs with a hard thick-walled light yellow putamen.

Odor: Offensive.

Taste: Astringent in taste, sweet in the post-digestive effect and has hot potency.

Size: 1.3 to 1.9 cm in diameter.

Fig. 9.90: Bahera fruits

Shape: Dry fleshy drupe, globose or ovoid.

Extra features: Fruits are hard due to its endocarp and it exhibits a yellow internal surface projecting threads which represents vascular bundles.

Chemical constituents: The fruit contains moisture 6%, tannin 21% (which comprises both condensed and hydrolysable types), water extractable 44%. Fruits contain a green fixed oil, saponin, tannins, a resitious residue and three amorphous and hygroscopic glycosidal compounds. The fruit pulp contains a non-nitrogenous crystalline substance. Kernles yield yellow fatty oil containing fatty acids. The seeds contain protein and oxalic acid, while bark contains tannin. Its oil contains palmitic, oleic and linoleic acids as major fatty acids, A new cardiac glycoside-bellericnin isolated which yielded glucose and galactose (2:1) sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid isolated from fruits.

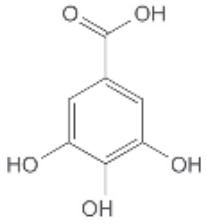


Fig. 9.91: Gallic acid

Chemical Test

Test for gallic acid: They give blue color when treated with ferric chloride solution.

Uses: The dried fruits of the tree constitute the drug bhaeda. The fruits are useful in stomach disorder such as indigestion, diarrhea. It is given also as a brain tonic and is applied on eyes as a soothing lotion. Baheda is useful in piles, leprosy, dropsy and fever. The half-dried fruits are considered to be purgative but the ripe and dried fruits have the opposite property. The baheda fruit is one of the three constituents of the triphala.

MYROBALAN

Synonyms: **Bengali:** Haritaki, Harida, **Hindi:** Harad, Harar, **English:** Chebulic myrobalan.

Biological source: It consists of dried, ripe and fully matured fruits of *Terminalia chebula* retzr belonging to family combretaceae.

Habitat: Organic chebula is found all over India from eastern to western region.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order Myrtales
- Family: Combretaceae
- Genus: *Terminalia*
- Species: *T. chebula*

Organoleptic Characters

Color: Yellowish brown

Odor: Odorless

Taste: Astringent, slightly bitter and sweetest at the end.

Size: 20 to 25 mm long and 15 to 25 mm wide.

Shape: Ovate and wrinkled longitudinally.

Extra features: The fruits are hard and stony with single seed which is yellow in color and 15 to 320 mm in length. The pulp of fruit is non-adherent to the seed.

Fig. 9.92: Myrobalan fruits

Chemical constituents: Myrobalan fruits are the important source of tannin. The tannin of myrobalan is pyrogallol type (hydrolysable tannin) choplogic acid, chebulinic acid and corilagin are the hydrolysable tannin while cherubic acid, ellagic acid and gallic acid are the other contents. It also contains glucose, orbital, gentiobiose and other sugars in traces.

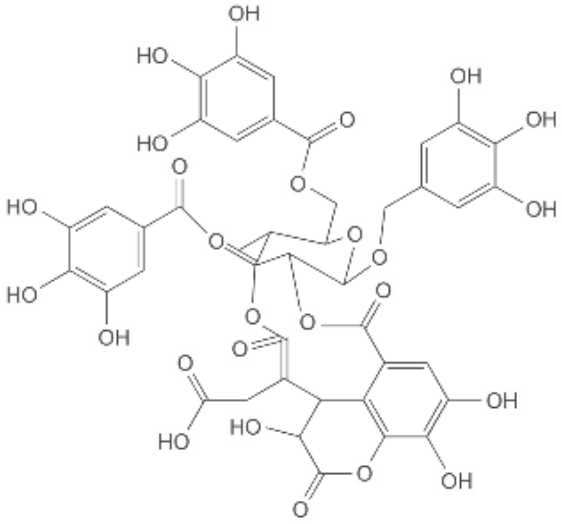


Fig. 9.93: Chebulinic acid

Standards:

- Foreign matter: NMT 2.0%
- Total ash: NMT 5.0%
- Acid insoluble ash: NMT 2.0%
- Alcohol soluble extractive: NLT 35.0%
- Water soluble extractive: NLT 32.0%
- Loss on drying: NMT 11.0%

Chemical test: Alcoholic/aqueous solution of myrobalan treated with 10% ferric chloride gives deep blue color and with lead acetate gives white precipitate.

Uses: *Terminalia chebula* is used to treat many diseases such as digestive diseases, urinary diseases, diabetes, skin diseases, parasitic infections, heart diseases, irregular fevers, flatulence, constipation, ulcers, vomiting, colic pain and hemorrhoids. It promotes wisdom, intellect and eyesight. *Terminalia chebula* has a strong effect against the herpes simplex virus HSV, has antibacterial activity and exhibits strong cardio tonic properties. It is good anti-oxidant also.

CATECHU

Synonyms: **Hindi:** Katha, khair, **Bengali:** Khayera, **Gujarati:** Kher, **Telugu:** Kachu.

Biological source: Black catechu consists of dried bark or dried aqueous extract of heart-wood of *Acacia catechu* belonging to family leguminosae.

Pale catechu consists of leaves and young shoots of *Uncaria gambier* rox family rubiaceae. The pale catechu is differentiated by black one by its pale color and light weight.

Habitat: Widely distributed in East Africa, Andhra Pradesh, Bihar, Punjab and Himalayas.

Botany:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Liliopsida
- Order: Arecales
- Family: Leguminosae
- Subfamily: Arecoideae
- Genus: *Acacia*
- Species: *Catechu*

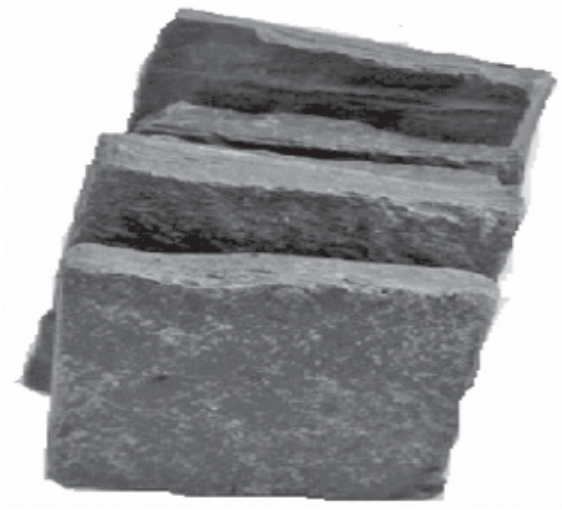


Fig. 9.94: Catechu

Organoleptic Characters

Color: Light brown to black

Odor: None

Taste: Astringent

Shape: Cubes or irregular fragments

Size: 2 to 5 cm

Extra features: Pieces are friable, porous with vegetable debris, fracture short soluble in water and alcohol.

Chemical constituents: Main chemical constituents of heartwood are tannins—condensed tannins, catechin (2–12%), catechuic acid, pyrocatechin, epicatechin, dicatechin, phloroglucin, protocatechuic acid, quercetin, gum, kaempferol, gossyptin and mineral.

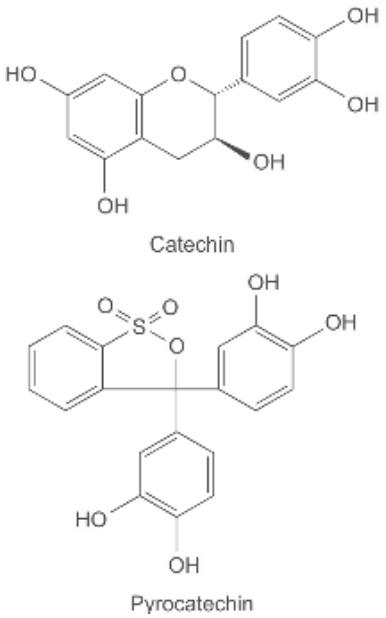


Fig. 9.95: Chemical constituents of catechu

Chemical test:

- **Gambier fluorescin test:** The powdered drug is boiled with alcohol and filtered and to the filtrate solution of NaOH is added stirred and a few ml of light petroleum is added. The petroleum layer shows green fluorescence. Black catechu does not respond to this test.
- Catechu gives bluish black color with ferric chloride solution.
- Pink and red color with vanillin and HCl.
- Brown color with lime water.

Standards:

- Total ash: NMT 6.0%
- Acid insoluble ash: NMT 3%
- Alcohol soluble extractive: NLT 40.0%
- Water soluble extractive: NLT 50.0%

Uses:

1. It is useful in stomach problems like diarrhea, dysentery, colitis and gastric cancer.
2. It is used as mouthwash for mouth, gum and throat diseases like gingivitis, stomatitis.
3. It is used in high blood pressure.
4. It is used as astringent and helpful in pharyngitis, and haemorrhages.

Substitutes and adulterants: *Rhizovhora mangle* linn, *ceriops candolleana* Arnold family rhizophoraceae.

LIPIDS, FATS AND WAXES

Lipids contain the elements carbon, hydrogen and oxygen but have a lower proportion of oxygen in the molecule than carbohydrates. With the exception of glycerol they are insoluble in water, but dissolve in organic solvents such as ether, chloroform and benzene. They are lighter (less dense) than water.

Classification of Lipids

1. ***Simple lipids:*** Esters of fatty acids with various alcohols.

a. **Fats and oils:** Chemically fats are triesters of glycerols and fatty acids. Fats may be either solid or liquid at room temperature. **Oils** are fats that are liquid state at normal room temperature.

b. **Waxes:** Chemically waxes are esters of fatty acids with higher molecular weight monohydric alcohols as cetyl alcohol ($C_{16}H_{33}OH$) or cholesterol. It is a mixture of long-chain apolar lipids forming a protective coating

Table 9.13: Functions of lipids with examples

S. No.	Functions of lipids	Examples
1.	Cell membrane components	Phospholipids, glycolipids, cholesterol
2.	Fat transporters	Lipoproteins (e.g. like high density and low-density lipoproteins)
3.	Storage of excess energy	FAs in TAGs
4.	Thermal insulation	Nonpolar lipids
5.	Major source of caloric energy	
	Energy source as a mobile respiratory substrate	Glycerol, fatty acids
	Energy store as a insoluble respiratory substrate	Fats in animal, oils in plants (seeds)
6.	Essential for normal growth and function	Docosahexaenoic acid (DHA for brain development)
7.	Precursors of hormones, coenzymes and chemical mediators	Vitamins (A, D, E, K), prostaglandins, thromboxanes, prostacyclins.
8.	Bioeffectors/Bioregulators	Phosphatidylinositol
9.	Others	As enzyme cofactors in electron carriers, as light-absorbing pigments, as fat-soluble vitamins (terpenes)
		Intracellular messengers and hydrophobic anchors which provide buoyancy in aquatic animals (fats). Waxes act as an waterproofing material on the surface of leaves and insects

(cutin in the cuticle) on plant leaves and fruits but also in animals. Example: Cetyl, meryl, merecyl alcohol.

2. ***Compound (or complex) lipids:*** Esters of fatty acids with alcohol containing additional groups such as phosphate, nitrogenous base, carbohydrates or protein, etc.

a. **Phospholipids: Chemically.** The glycerol forms ester links with two fatty acid molecules and with one phosphate group. The phosphate group can ionise (become polarised) and so becomes water soluble but the fatty acid tails are non-polar and remain water insoluble. The possession of both hydrophilic and hydrophobic groups is a very important biological property. Sphingophospholipids are phospholipids with sphingosine as alcohol, e.g. sphingomyeline.

b. **Glycolipids (glycosphingolipids):** Glycolipids (molecular complexes of lipid and polysaccharides) are found on the outside of cell membranes as the glycocalyx. This is involved in cell to cell recognition and communication, particularly during growth and development. They may also be used as infection sites by viruses and bacteria.

3. ***Derived lipids:*** These include by-products of metabolic processes like fatty acids, glycerol, mono- and diacylglycerols, lysophosphatides, fatty aldehydes, ketone bodies.

4. ***Steroid lipids:*** Cholesterol, cholesteryl esters, cholesterol derivatives—bile acids, steroid hormones, vitamin D, phytosterols. Because they are uncharged, also they are termed **neutral lipids**.

5. ***Miscellaneous lipids:*** Aliphatic hydrocarbons, carotenoids, squalene, terpenes (composed of isoprene units), vitamins E and K, glycerol ether, glycosyl glycerols (in plants)
Analytical parameters for fats and oils:

- *Physical constants:* Viscosity, specific gravity, refractive index, solidification point.
- *Chemical constants:* Iodine value, acid value, peroxide value, saponification value, unsaponifiable matter.

The brief idea of some analytical parameters of chemical constant is as follows:

Iodine value: Iodine number is the determination of the amount of unsaturation contained in fatty acids. The iodine value (or "iodine adsorption value" or "iodine number" or "iodine index") is the mass of iodine in grams that is consumed by 100 grams of a chemical substance.

Acid value: Acid value (or "neutralization number" or "acid number" or "acidity") is the mass of potassium hydroxide (KOH) in milligrams that is required to neutralize one gram of chemical substance. The acid number is a measure of the amount of carboxylic acid groups in a chemical compound, such as a fatty acid, or in a mixture of compounds.

Acid value

$$= \frac{\text{Volume (ml) of 0.1 mol/l ethanolic potassium hydroxide consumed}}{\text{Weight (g) of the sample}} \times 5.611$$

Peroxide value: Peroxide value is defined as the milliequivalents of peroxidises per kilogram of sample. It is used as a measurement of the extent to which rancidity reactions have occurred during storage.

Saponification value: Saponification value (or "saponification number") represents the number of milligrams of potassium hydroxide or sodium hydroxide required to saponify 1 g of fat under the conditions specified. It is a measure of the average molecular weight (or chain length) of all the fatty acids present.

Saponification value

$$= \frac{(a - b) \times 28.05}{\text{Weight (g) of the sample}}$$

where, a = volume (ml) of 0.5 mol/l hydrochloric acid consumed in the blank test,

b = volume (ml) of 0.5 mol/l hydrochloric acid consumed in the test.

Unsaponifiable matter: Unsaponifiables are components of an oily (oil, fat, wax) mixture that fail to form soaps. It inculdes sterols, oil soluble vitamin, hydrocarbons and higher alcohols.

Ester value: The ester value is the number of mg of potassium hydroxide (KOH) required to saponify the esters in 1 g of a sample.

Ester value = Saponification value * Acid value

Hydroxyl value: The hydroxyl value is the number of mg of potassium hydroxide (KOH) required to neutralize acetic acid combined to hydroxyl groups.

$$\text{Hydroxyl value} = \frac{(a - b) \times 28.05}{\text{Weight (g) of the sample}} + \text{acid value}$$

where, a = volume (ml) of 0.5 mol/l ethanolic potassium hydroxide consumed in the blank test,

b = volume (ml) of 0.5 mol/l ethanolic potassium hydroxide consumed in the test.

CASTOR OIL

Synonyms: Palma christi. Castor oil bush.

Biological source: Castor oil is obtained from seeds of *Ricinus communis.* Family: Euphorbiaceae.

Habitat: By cultivation it has been distributed through not only all tropical and subtropical regions, but also in many of the temperate countries of the globe.

Fig. 9.96: Castor oil

Botany:

- Kingdom: Plantae
- Phylum: Magnoliophyta
- Class: Magnoliopsida
- Order: Malpighiales
- Family: Euphorbiaceae
- Subfamily: Acalyphoideae
- Genus: *Ricinus*
- Species: *Communis*

Parts used: Processed seed oil.

Organoleptic Characters

Color: Viscid fluid, almost colorless.

Odor: Slight odor.

Taste: Nauseous and disagreeable taste.

Specific gravity: 0.96

Solubility: It dissolves freely in alcohol, ether and glacial acetic acid.

Chemical constituents: Castor oil consists chiefly of the glycerides of ricinoleic, isoricinoleic dihydroxy-stearic, and other acids. **Ricinolein** is the chief constituent of castor oil and is the triglyceride of ricinoleic acid.

Chemical test: 10 ml of castor oil with 5 ml of light petroleum shows a clear solution. If light petroleum is increased to 15 ml, the mixture becomes turbid.

Uses: Castor oil is a well-known cleansing laxative and purgative. It is sometimes used to treat food poisoning. Externally it is used for warts, fibroid cysts, appendicitis, sores, abscesses, and neuralgia. Castor oil is also the source for undecylenic acid, a natural fungicide.

Table 9.14: Average composition of castor seed oil/ fatty acid chains

Acid name	Average percentage range
Ricinoleic acid	85 to 95%
Oleic acid	6 to 2%
Linoleic acid	5 to 1 %
Linolenic acid	1 to 0.5 %
Stearic acid	1 to 0.5 %
Palmitic acid	1 to 0.5 %
Dihydroxystearic acid	0.5 to 0.3 %
Others	0.5 to 0.2 %

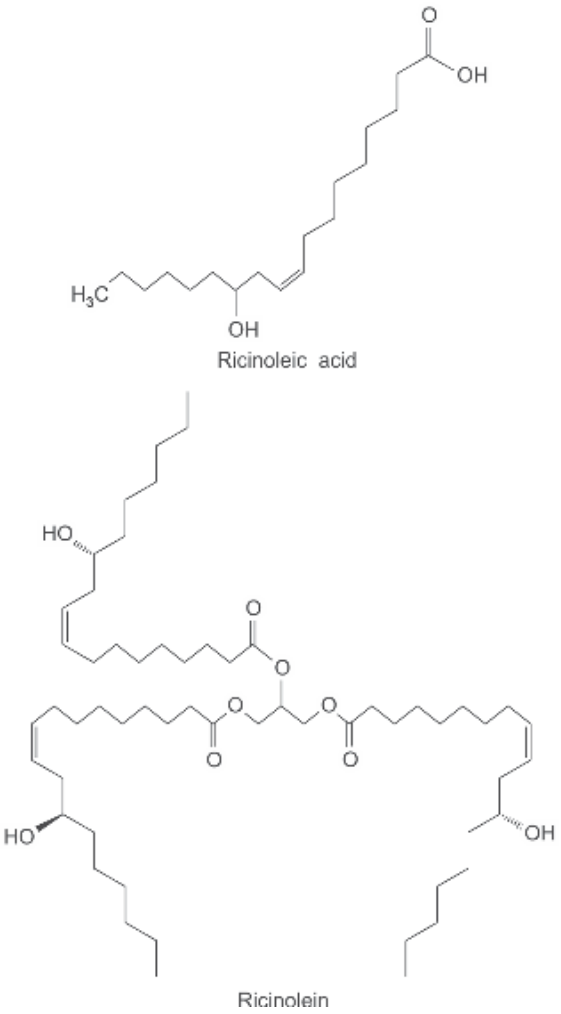


Fig. 9.97: Chemical constituents of castor oil

LINSEED OIL

Synonyms: **Hindi:** Alsi, **English:** Flax seeds.

Biological source: It consists of dried ripe seeds of *Linum usitatissimum* Linn, containing NLT 25% of fixed oil, family Linaceae.

Habitat: Linseed is cultivated in many subtropical countries such as South America, India, USA, Canada, England, Russia, Greece, Italy and Spain.

Botany:

- Kingdom: Plantea
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Malpighiales
- Family: Linaceae
- Genus: *Linum*
- Species: *Usitatissimum*

Parts used: Dried ripe seeds

Organoleptic Characters

Color: Brown

Odor: Odorless

Taste: Mucilaginous, oily

Size: 4–6 mm long, 1–2 mm thick

Shape: Elongated-ovoid, flattened.

Extra features: Testa is hard, smooth and glossy in appearance.

Characters of Oil

- **Color:** Pale yellow clear liquid.
- **Taste:** Disagreeable but bland taste.
- **Solubility:** Slightly soluble in alcohol, soluble in organic solvents, insoluble in water.
- **Acid value:** NMT 4
- **Unsaponifiable matter:** NMT 1.5
- **Iodine value:** 160–200
- **Saponification value:** 188–195
- **Specific gravity:** 0.977 to 0.931
- **Refractive index:** 1.478 to 1.482

Chemical constituents: Linseed seeds contain fixed oil (30–40%), mucilage (6%), protein (25%), small amount of enzyme lipase and linamarin. Carbohydrates present are sucrose, raffinose, cellulose and mucilage.

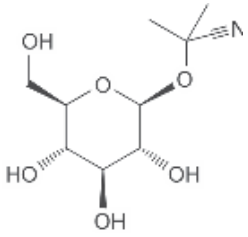


Fig. 9.98: Linamarin

Table 9.15: Average composition of linseed seed oil

Acid name	Average % range
Palmitic acid	6 %
Oleic acid	18.5 to 22.6 %
Stearic acid	2.5 %
Arachidic acid	0.5
Linoleic acid	24.1
Alpha-linolenic acid	47.4
Other	0.5

Chemical test: With ruthenium red it gives red color.

Uses: Used to make demulcent and in constipation. Linseed oil has emollient, expectorant, diuretic, demulcent and laxative properties. Treated linseed oil is also added to things like paints, resins, varnishes, and inks. Painters use linseed oil as a carrier oil for their paints.

Adulterants: Linseed oil is adulterated with vegetable oils such as rape, cottonseed, soyabean, sunflower and candlenut.

OLIVE OIL

Synonyms: Salad oil, sweet oil, oleum olival.

Biological source: Olive oil is a fixed oil obtained by expression of ripe fruits of *Olea europeana* linn, family oleaceae.

Habitat: California, Southern Australia.

Botany:

- Kingdom: Plantea
- Order: Lamiales
- Family: Oleaceae
- Genus: *Olea*
- Species: *European*

Parts used: Ripe fruits

Organoleptic Characters

Color: Yellowish to greenish yellow.

Odor: Slight and characteristic.

Taste: Bland and faintly acrid.

Size and shape: Liquid.

Chemical constituents: It contains mixed glycerides of oleic acid (83.5%), palmitic acid

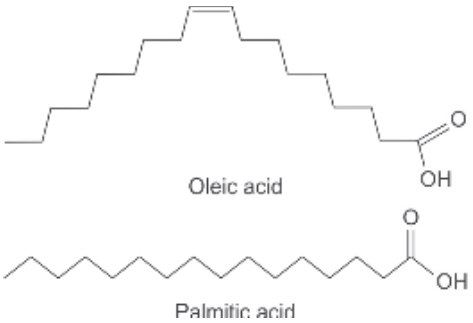


Fig. 9.99: Chemical constituents of olive oil

(9.4%), linoleic acid (7%), stearic acid (2%) and arachidic acid (0.9%). Along with traces of squalene (up to 0.7%) and sterols (about 0.2% phytosterol and tocosterols. Olive oil contains a group of related natural products with potent antioxidant properties which give extra-virgin unprocessed olive oil, it is bitter and pungent taste and which are esters of tyrosol and hydroxy-tyrosol, including oleocanthal and oleuropein.

Characters of Olive Oil

- **Color:** Pale yellow or light greenish yellow.
- **Taste:** Bland and acrid taste.
- **Odor:** Acrid taste.
- **Solubility:** Slightly soluble in alcohol, miscible with ether, chloroform and carbon disulphide.
- **Acid value:** 0.2–2.8
- **Iodine value:** 79–90
- **Saponification value:** 187–196
- **Specific gravity:** 0.914 to 0.919
- **Refractive index:** 1.478 to 1.482

Chemical test: Under ultraviolet radiation, it gives deep yellow coloration.

Uses: Emollient and soothing agent, demulcent, mild laxative and nutritive.

COD LIVER OIL

Synonyms: **Latin:** *Oleum morrhuae*, **English:** Cod liver oil.

Biological source: A fixed oil obtained from the fresh livers of *Gadus morrhua* and other species of Gadus., family Gadidae.

Habitat: Oil is produced mainly in Western Europe, including Germany and Denmark.

Botany:

- Kingdom: Animalia
- Phylum: Chordata
- Class: Actinopterygii
- Order: Gadiformes
- Family: Gadidae
- Genus: *Gadus*
- Species: *Morrhua*

Organoleptic Characters

Color: Pale yellow

Odor: Fishy odor

Taste: Fishy taste

Chemical constituents: It has high levels of the omega-3 fatty acids, EPA and DHA, and very high levels of vitamins A, D and E. It is widely taken to ease the symptoms of arthritis as well as other health benefits. It also contains unsaturated acid (85%) and saturated acid (15%).

Characters of Cod Liver Oil

- **Color:** Pale yellow
- **Taste:** Slightly fishy
- **Odor:** Fishy and not rancid
- **Solubility:** Sparingly soluble in alcohol, readily soluble in ether and chloroform.
- **Iodine value:** 159–173.

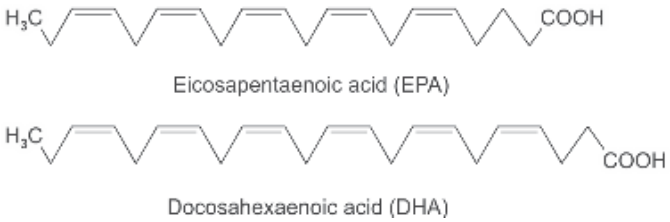


Fig. 9.100: Chemical constituents of cod liver oil

Chemical Test

Test for vitamin A: In 1 ml of chloroform, dissolve the quantity equal to 10–15 units of vitamin A and add 5 ml of antimony trichloride solution, a transient blue color is produced.

Test for vitamin D: In 1 ml chloroform dissolve the quantity equal to 1000 units of vitamin D and add 10 ml of antimony trichloride solution, a pinkish red color appears.

Uses: Emollient, nutrient, tonic, alterative. It is employed in the treatment of tuberculosis, chronic bronchitis, rachitis, etc. Sometimes used externally for chronic skin diseases, as eczema.

Adulterants and substitutes: Cod liver oil is adulterated with other fish-liver oils and seal oil. Halibut liver oil is a fixed oil prepared from the livers of halibut, *Hippogolossus vulgaris*, Family: Pleurnectidae. It has a lot of vitamins A and D.

NEEM OIL

Synonyms: Margosa, Neem, Nim tree.

Biological source: Neem oil is botanical oil, extracted from seeds and kernels of neem tree (*Azadirachta indica*), a member of the meliaceae family.

Habitat: South East Asia, India, Pakistan, Sri Lanka, Burma and Malaya.

Parts used: Seeds and kernels.

Organoleptic Characters

Nature: Hydrophobic

Color: Light to dark brown

Odor: Strong odor (like peanut and garlic)

Taste: Bitter

Solubility: Slightly soluble in water

pH: 6.5 to 7.5

Extra characters: It boils at more than 200°C and freeze at 13°C.

Chemical constituents: It comprises mainly triglycerides and large amounts of triterpenoid compounds, which are responsible for the bitter taste. Neem oil also contains steroids (campesterol, beta-sitosterol, and stigmasterol) and a plethora of triterpenoids. Most active compound in neem oil is Azadirachtin A and B, out of which Azadirachtin A is more active and is in abundance. Active ingredient in neem oil includes nimbin, meliantriol, salanin, meldenin, azadiradione, azadirone, isonimolicinolide, mahmoodin, nimbidinin, nimbonin, vepinin, etc.

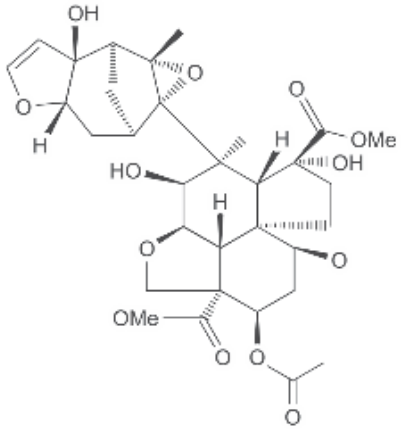


Fig. 9.101: Azadirachtin

Methods of extraction: The methods used for extraction is pressing (expelling) or solvent extraction. The oil can be obtained through pressing (crushing) of the seed kernel through cold pressing. Neem seed oil can also be obtained by solvent extraction of the neem seed, fruit, oil, cake or kernel.

Chemical Test

Test for terpenoids (Salkowski test): 5 ml of oil mixed in 2 ml of chloroform, and concentrated H_2SO_4 (3 ml) added to form a layer. A reddish brown coloration of the interface will be formed to show positive results for the presence of terpenoids.

Uses:

1. Neem oil is widely used in crop protection against insects, pests, nematodes, fungi, virus.

2. Neem oil is used as veterinary medicines for pets.
3. Neem oil is used for preparation of various cosmetic and toiletries.

COCOA BUTTER (THEOBROMA OIL)

Synonyms: Cacao butter, cocoa butter, semina theobromatis.

Biological source: Theobroma oil is obtained by expression of ground kernels of *Theobroma cacao* linn (family sterculiaceae).

Habitat: The chocolate tree (cocoa tree) is a native of tropical America and cultivated in Ecuador, Mexico, Central America, Sri Lanka, south India and Odisha.

Botany:

- Kingdom: Plantae
- Order: Malvales
- Family: Malvaceae
- Genus: *Theobroma*
- Species: *Cacao*

Parts used: Seeds

Organoleptic Characters

Color: Seed coat is chocolate brown in color

Odor: Chocolate

Taste: Chocolate

Size: 15 mm wide and 7 mm thick

Shape: Flattened-ovoid

Fig. 9.102: Cocoa butter

Extra features: The kernel consists of two irregularly folded, chocolate colored cotyledons.

Extraction of cocoa butter: Cocoa beans are ground into chocolate liquor and pressed to separate the cocoa butter from the cocoa solids. Cocoa butter can alternately be extracted from whole beans by the broma process. It is most often deodorized to remove its strong and undesirable taste.

Characters of Cocoa Butter

- **Color:** Yellowish white solid
- **Taste:** Chocolate odor
- **Odor:** Chocolate taste
- **Solubility:** Slightly soluble in alcohol, soluble in boiling alcohol, very soluble in ether, benzene and chloroform
- **Melting point:** 30°–35°C

Chemical constituents: Cocoa butter consists of the glycerides of stearic (34%), palmitic (26%), arachidic, oleic (37%) and other acids. The seeds contain fixed oil (35–50%), starch (15%), theobromine (1–4%), caffeine (0.36%), proteins (15%), sugar, cacao-red, volatile odorous principle and ash.

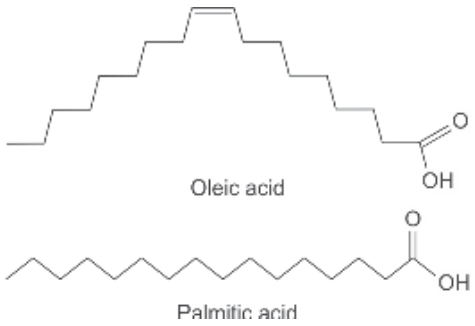


Fig. 9.103: Chemical constituents of cocoa butter

Chemical test: Dissolve 1 gm of theobroma oil in 3 ml of ether in a test tube at temperature 17°C. Immerse the test tube in cold water. The solution does not become turbid or deposit while flexes in less than 3 minutes. After congealing rays the temperature up to 15°C clear liquid is gradually formed.

Uses: Because of the low melting point of cocoa butter, it is often used in pharmaceuticals as a base for suppositories. Cocoa butter is one of the most stable fats known, containing natural antioxidants. The smooth texture, sweet fragrance and emollient property of cocoa butter make it a popular ingredient in cosmetics.

Adulterants: Waxes, stearin-like coconut stearin or animal and vegetable tallows.

WOOL FAT

Synonyms: Adeps lanae, wool wax, wool fat, anhydrous wool fat or wool grease.

Biological source: Wool fat is a fatty, purified and anhydrous waxy substance secreted by the hairs constituting the fleece of the sheep *Ovis aries*, linn family bovidae.

Habitat: Australia, USA, India (lesser extend).

Botany:

- Kingdom: Animalia
- Phylum: Chordata
- Class: Mammalia
- Order: Artiodactyla
- Family: Bovidae
- Genus: *Ovis*
- Species: *Aries*

Extraction of wool fat: Wool fat is extracted by scouring the fleeces with hot water, and allowing the emulsion thus produced to stand, when impure wool fat rises as a cream. This can be cleansed by repeatedly mixing with water and separating by centrifugation, the resulting wool fat being subjected to a final process of purification.

Characters of Wool Fat

- **Color:** Pale yellow.
- **Taste:** Chocolate odor.
- **Odor:** Faint characteristic.
- **Solubility:** Insoluble in water, sparingly soluble in cold alcohol.
- **Melting point:** 42ºC.
- **Storage:** Temperature not exceeding 25ºC.

Chemical constituents: Wool fat consists chiefly of cholesteryl and iso-cholesteryl alcohols combined with lanoceric, lanopalmitic, carnaubic, myristic, a little oleic, and possibly also palmitic and cerotic acids.

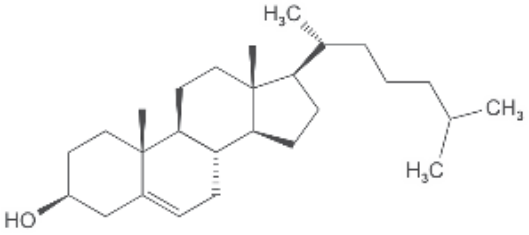


Fig. 9.104: Cholesteryl alcohol

Chemical Test

For cholesteryl alcohol: Dissolve 0.1 gramme in a mixture of 5 c.c. of chloroform and 0.5 c.c. of acetic anhydride; pour gently upon 5 c.c. of sulphuric acid; a purplish brown ring, passing into green is developed at the surface of contact.

Uses: Wool fat is largely used as an emollient and for promoting the absorption of drugs by the skin.

Adulterants: The most probable adulterants of wool fat are mineral fats (soft paraffin) or animal and vegetable fats and oils.

LARD

Synonyms: Adeps.

Biological source: Lard is the purified fat from the abdomen of the hog, *Sus scrofa* Linn., Family Suidae.

Botany:

- Kingdom: Animalia
- Phylum: Chordata
- Class: Mammalia
- Order: Unigulata
- Family: Suidae
- Genus: *Sus*
- Species: *Scrofa*

Parts used: Abdomen of hog.

Extraction of lard: Lard may be rendered by either of two processes, wet rendering or dry rendering.

Wet rendering: The pig fat is boiled in water or steamed at a high temperature and the lard, which is insoluble in water, is skimmed off the surface of the mixture, or it is separated in an industrial centrifuge. Wet-rendered lard has a more neutral flavor, a lighter color, and a high smoke point.

Dry rendering: The fat is exposed to high heat in a pan or oven without the presence of water. Dry-rendered lard is somewhat more browned in color and flavor and has relatively lower smoke point.

Properties of Lard

- **Color:** Soft white
- **Odor:** Not rancid
- **Melting point:**
  - Back fat: 30–40°C
  - Leaf fat: 43–48°C
  - Mixed fat: 36–45 °C
- **Specific gravity:** 0.917–0.938
- **Iodine value:** 45–75
- **Acid value:** 3.4
- **Saponification value:** 190–205

Chemical constituents: The lard consists of: Saturated fats 38–43%, Palmitic acid: 25–28%, Stearic acid: 12–14%, Myristic acid: 1%, Unsaturated fats 56–62%, Monounsaturated fats 47–50%, Oleic acid: 44–47%, Palmitoleic acid: 3%, Linoleic acid: 6–10%.

Chemical Test

Saponification test for triglycerides: Add 25 ml of 10% NaOH to evaporated fat boil in boiling water bath for 30 min cool and add excess of Na_2SO_4 solution soap forms and raise at the top, filter it. To the filtrate add sulphuric acid evaporate and collect residue, the residue contains glycerol. Dissolve residue in ethanol. Ethanolic solution used to perform following test:

1. To the ethanolic solution add a few drops of copper sulfate and sodium hydroxide solution, clear blue color is observed.
2. To the ethanolic solution add a few crystals potassium hydrogen sulphate, heat it vigorously, pungent odor of acrylic aldehydes is produced.

Uses: Used in cooking, emollient, ointment base and protective. Lard oil is used as a antifoaming agent in fermentation and as tablet lubricants, illuminant and to manufacture soap.

CARNAUBA WAX

Synonyms: Palm wax, tree of life.

Biological source: Carnauba is a wax derived from the leaves of the carnauba palm, *Copernicia cerifera* belonging to family Palmae.

Habitat: A plant native to and grown only in the northeastern Brazilian states.

Organoleptic Characters

Color: Hard greenish yellow wax.

Odor: No odor.

Taste: No taste.

Melting point: 50–56°C.

Compatibility: Carnauba wax is compatible with most animal, vegetable and mineral waxes and a large variety of natural and synthetic resins.

Extra features: Commercially available in form of flakes.

Chemical constituents: Carnauba wax contains mainly esters of fatty acids (80–85%), fatty alcohols (10–16%), acids (3-6%) and hydrocarbons (1–3%). Specific for carnauba wax is the content of esterified fatty diols (about 20%), hydroxylated fatty acids (about 6%) and cinnamic acid (about 10%). Cinnamic acid, an antioxidant, may be hydroxylated or methoxylated.

Chemical Test

Acid value: Weigh accurately 3 g into a 250 ml flask attached to a reflux condenser, add 50 ml of a mixture of isopropyl alcohol and toluene (5:4), and boil gently until the wax is completely dissolved. Remove the flask from the condenser, add about 1 ml of phenolphthalein, and immediately titrate with 0.5 n alcoholic potassium hydroxide to a faint, reddish yellow color. Calculate the acid value as the number of Mg of potassium hydroxide required to neutralize the free acids in 1 g of carnauba wax. The acid value so obtained is between 2 and 7.

Saponification value: To the solution from the test for *acid value* add 15.0 ml of 0.5 n alcoholic potassium hydroxide, reflux for 3 hours, and titrate the excess alkali with 0.5 n hydrochloric acid to a yellow-amber color. Perform a blank determination. The saponification value is between 78 and 95.

Residue on Ignition: Heat 2 g in an open porcelain or platinum dish over a flame, it volatilizes without emitting an acrid odor. Ignite the weight of the residue does not exceed 5 mg. Not more than 0.25% is found.

Uses: Cosmetics, glamour products, pharmaceuticals, ointments, tablet coatings, candles, confections, investment casting, auto, floor and shoe polishes, carbon paper, inks, paper coatings and fruit coatings.

BEESWAX

Synonyms: Yellow beeswax, white beeswax, cera flava, cara alba.

Biological source: Beeswax is wax separated from the honeycomb of hive bees *Apis mellifera* linn, family apidae. All bees make wax in epidermal glands to cover their outer layer of cuticle to prevent water loss.

Habitat: West Indies, California, Jamaica, Chili, Egypt, Syria, Morocco.

Preparation of Beeswax

Yellow beeswax: After collecting honey from honey comb, the comb is melted in water so that impurities and residual honey settle down. After straining wax mixture is allowed to cool, remelted and finally strained to collect yellow beeswax.

White beeswax: It is prepared by process of bleaching by use of chemicals (charcoal, potassium permanganate, chromic acid, ozone, chlorine or treatment with hydrogen peroxide) or by use of light, air and water, ribbon-like strips of waxes is formed till bleaching is complete.

Characters of Beeswax

- **Color:** Yellowish to brownish yellow
- **Odor:** Honey-like odor
- **Taste:** Balsamic taste
- **Melting point:** 62–65°C
- **Density:** 0.95–0.96
- **Solubility:** Practically insoluble in water, slightly soluble in cold alcohol, soluble in hot alcohol, chloroform, benzene and ether.
- **Saponification value:** 3–5.

Chemical constituents: The wax contains an ester myricin (78%), free wax acids (14%), moisture and cerolein (aromatic substance). The color of wax is due to presence of pollen pigments and propolis.

Chemical test: Boil 0.5 gm of beeswax with 20 ml of aqueous caustic soda solution for 10 minutes cool, content is cooled and filtered. The filtrate on treatment with HCl gives clear solution. No turbidity is produced.

Uses: Beeswax is used commercially to make fine candles, cosmetics and pharmaceuticals including bone wax. It is also used as a coating for cheese. Beeswax is also an ingredient in moustache wax, as well as hair pomades.

Adulterants: Solid paraffin, ceresin, various fats and waxes of vegetable or animal origin with resin and stearic acid.

Marine Drugs

"It is said that life started in the seas, and many researchers feel that the sea holds the secret to life itself."

Marine biotechnology is the science in which marine organisms are used in full or partially to make or modify products, to improve plants or animals or to develop microorganisms for specific uses. Approximately 70% of the Earth's surface is covered with water. The sea holds an endless source of life. Approximately 85% of water is seawater, which contains sodium chloride and trace minerals. Only 10% of over 25,000 plants have been investigated for biological activity. The marine environment may contain over 80% of world's plant and animal species. In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, sea hares, nudibranchs, bryozoans, sea slugs and marine organisms. With the help of different molecular and biotechnological techniques, humans have been able to elucidate many biological methods applicable to both aquatic and terrestrial organisms.

There are several phyla of marine flora (algae) to be discussed, including:

1. **Phaeophyta** (*Benthic Brown Algae*): Xanthophyll fucoxanthin.
2. **Rhodophyta** (*Red Algae*): Color comes from red pigments, Xanthophylls.
3. **Chlorophyta** (*Green Algae*): Predominantly found in fresh water and also in salt water.

Table 9.16: Marine drugs with chemical constituents and uses

S. No.	Botanical name	Chemical constituents	Uses
1.	*Ascophyllum nodosum*	Alginic acid (a polysaccharide)	Suspending agent protective colloid used in cosmetics, shampoos, creams, lotions, and ointments.
2.	*Alaria esculenta*	Vitamins (E, C, B12, B6, B3, B, A): Minerals (Zn, F, Cr, Co, Mn, I, Na, Fe, P, Mg, K, Ca), fat, protein, and carbohydrates	Used in cosmetic and hair care products
3.	*Laminaria longicruris*	Calcium, potassium, iodine, mannitol, and glutamic acid, and contains the same vitamin and mineral group	Antioxidative activity
4.	*Palmaria palmata*	Minerals, particularly fluoride, phosphorus, potassium	Used in chowders, salads, etc.
5.	*Porphyra umbilicalis*	Vitamins A, B, B2, B3, B6, B12, C	Used both in hair and skin treatment products
6.	*Sargassum fluitans*	C12–C20 saturated fatty acids (arachidonic, oleic, palmitic, myristic, and lauric acids).	Used in the treatment of goiters and lithiasis anticoagulant properties
7.	*Eisenia bicyclis*	Enzyme B-glucuronidase	Anti-inflammatory
8.	*Fucus vesiculosus* L	Polysaccharides and polyphenols, phlorotannins, polyphenols,	Used internally for obesity, rheumatism, and as a massage for cellulite
9.	*Chlorella vulgaris*	60% protein essential amino acids	Good source of chlorophyll used as a blood builder
10.	*Spirulina*	Protein (55 to 70%), carbohydrates (15 to 25%), lipids (4 to 7%), and minerals (5 to 10%)	It is a good source of vitamins and enzymes
11.	*Chondrus crispus*	Mucilage, polysaccharides (carrageenans), sulphur compounds, protein, iodine, bromine, iron	Used as a thickener and stabilizer used to treat and soothe sore throats

Table 9.17: Metabolites from marine cyanobacteria

S. No.	Metabolites/biological source	Activity
1.	Carotenoids and phycobiliprotein pigments from cyanobacteria	Natural food coloring agents, as feed additives, as enhancers of the color of egg yolks, to improve the health and fertility of cattle, as drugs and in the cosmetic industries
2.	*Lyngbya lagerhaimanii* and *phormidium tenue*	Anti-HIV activity
3.	*Fusarium chlamydosporum* isolated from the Japanese marine red alga *carpopeltis affinis*	Activity against a variety of microorganisms and microalgae
4.	Cyanobacterium *stigonema* spp	Anti-inflammatory and anti-proliferative properties
5.	Dinoflagellate *goniodoma pseudogoniaulax*	An antifungal polyether macrolide
6.	*Gambierdiscus toxicus*	Antifungal agents

4. **Cyanophyta** (*blue green algae*): These contain chlorophyll and other pigments and are microscopic.
5. **Chrysophyta** (*golden brown algae*): Predominantly found in fresh water, and sometimes in seawater.
6. **Dinophyta** (*pyrrophyta*): These are usually found in the phytoplankton and are microscopic.
7. **Xanthophyta** (*yellow green*): Fresh water, high in carotenoids.
8. **Cryptophyta:** Contain green, blue, and red pigments.
9. **Haptophyta:** A relatively new division of what was formerly thought as chrysophyta.
10. **Bacillariophyta** (Diatoms): Contain silica cell walls. These cell walls are resistant.

"Poison kills the poison," the famous proverb is the basis for researchers in finding the biomedical metabolites from living organisms. Sea has got plenty of metabolites and other resources in living or dead form. Sponges (37%), coelenterates (21%) and microorganisms (18%) are the major sources of biomedical compounds followed by algae (9%), echinoderms (6%), tunicates (6%), molluscs (2%), bryozoans (1%), etc. More than 50% of the 100 isolates from marine sources are potentially exploitable bioactive substances.

Metabolites from Seaweeds

Seaweeds are abundant in the intertidal zones and in clear tropical waters. Marine algae have received comparatively less bioassay attention. In addition, there are a number of seaweeds with economic potential. It will be of great significance if these species could be the major role players in drug development.

Seaweeds are also much higher in protein than land vegetables. They are good sources of iodine and vitamins A, B2, B12, and C. Seaweeds are rich in compounds pertinent to

Table 9.18: Metabolites from seaweeds

S. No.	Metabolites/biological source	Activity
1.	Red alga *Sphaerococcuscoronopifolius*	Antibacterial activity
2.	Green alga *Ulva lactuca*	Anti-inflammatory activity
3.	*Portieria hornemannii*	Anti-tumor compound
4.	*Ulva fasciata*	Antiviral activity *in vivo*
5.	Brown alga *Stypodium zonale*	Anticancer activity
6.	*Codium iyengarii*	Antibacterial activity

Metabolites of this class occur in diseases such as psoriasis, asthma, arteriosclerosis, heart disease, ulcers and cancer, etc.

the cosmetic industry, such as ursolic acid derivates, fucose polymers, and polysaccharides.

- *Polygalactosides* react with the proteins in the outer surface of the skin and hair, ion–ion interactions form a protective moisturizing complex.
- *Fucose polymers* are very hygroscopic and act as hydrating agents.
- *Ursolic acid* and its derivates can form oil-resistent barriers on skin and hair, the same as they do in the waxy coating on apples, pears, cranberry, prunes, and other fruits.

Sea algae are rich in non-essential and essential amino acids (e.g. proline, glycine, and lycine). Elastic fibers in skin are also rich in these amino acids. Therefore, seaweed can play an important role in cosmetics as a moisturizing agent, helping to maintain the skin's elasticity by increasing its hydration.

Metabolites from Sponges

Approximately 10,000 sponges have been described in the world and most of them live in marine waters. A range of bioactive metabolites has been found in about 11 sponge genera. Three of these genera (*haliclona*, *petrosia* and *discodemia*) produce powerful anti-cancer, anti-inflammatory agents, but their cultivation has not been studied.

Table 9.19: Metabolites from sponges

S. No.	Metabolites/biological source	Activity
1.	*Cryptotethiacrypta*	Potent tumor-inhibiting arabinosyl nucleoside
2.	*Dercitus* spp. (aminoacridine alkaloid)	Cytotoxic activities
3.	Japanese sponge *theonella* spp (halichondrin-B)	Potential anticancer agent
4.	*Theonella* spp.	*In vitro* cytotoxity and *in vivo* antitumor activity
5.	*Caminus sphaeroconia*	Potent inhibitor ofthe bacterial type-III secretion system
6.	*Xestospongia berguista*	Antihistaminic activity
7.	Carribean sponge *Batzella* spp	Anti-HIV activity
8.	*Hyrtios erecta*	Anticancer activity

Table 9.20: Metabolites from cnidarians

S. No.	Metabolites/biological source	Activity
1.	*Lobophytum crassum*	Antibacterial activity
2.	*Pseudopterogorgia* (a tricyclic diterpene pentoside)	Anti-inflammatory and analgesic activities
3.	*Subergorgia suberosa* (sesquiterpene suberosols A–D)	Anti-inflammatory activity
4.	*Clavularia viridis* Clavubicyclone	Anticancer activity
5.	*Erythropodium caribaeorum* (diterpenes)	Antimitotic agents
6.	*Pseudopterogorgia elizabethae* (pseudopterosins)	Used in cosmetic industries
7.	*Eunicea fusca* (contains fucoside-A)	Used in cosmetic industries

Table 9.21: Metabolites from bryozoans

S. No.	Metabolites/biological source	Activity
1.	*Flustra foliacea* (deformylflustrabromine)	Moderate cytotoxicity
2.	*Watersipora subtorquata* (bryoanthrathiophene)	Anti-angiogenic activity
3.	*Bugula neritina* (bryostatin)	Anti-cancer activity
4.	*Cribricellina cribreria* (β-carboline alkaloid)	Cytotoxic, antibacterial, antifungal and antiviral activities

Table 9.22: Metabolites from mollusks

S. No.	Metabolites/biological source	Activity
1.	*Dolabella auricularia* (Dolastatin, a cytotoxic peptide)	Antineoplastic substance
2.	*Hexabranchus sanguineus (*Ulapualide-A, a sponge-derived macrolide)	Antifungal activity
3.	*Chromocloris cavae* Chromodorolide-A	*In vitro* antimicrobial and cytotoxic activities

Table 9.23: Metabolites for tunicates

S. No.	Metabolites/biological source	Activity
1.	*Halocynthia aurantium* (halocidin)	Antimicrobial peptide
2.	*Styela clava* clavaspirin	Antibacterial peptide
3.	*Didemnum* spp (alkaloids)	Antiplasmodial and antitrypanosomal activity
4.	*Eudistoma* species (eudistomins)	Potent antiviral activity *in vitro*

Metabolites from Fish, Sea Snakes and Marine Mammals

Metabolites extracted from fish, sea snakes and aquatic mammals are scanty. Various fish species are used to extract fish oil, rich in omega-3 fatty acids, which are used in the preparation of various kinds of drugs for the remedies of human beings, such as arthritis and many others. Throughout the world about 500 species of fish are considered toxic. The most spectacular substance of pharmacological importance extracted from fish is tetradotoxin (TTX), the puffer or fugu poison. Other toxins isolated include ciguatoxin from electric rays, which is served as a potent antidote for pesticide poisoning.

Marine Toxins

Marine animals may accumulate and use a variety of toxins from prey organisms and from symbiotic microorganisms for their own purposes. Thus, toxic animals are particularly abundant in the oceans. The toxins vary from small molecules to high molecular weight proteins and display unique chemical and biological features of scientific interest. Marine toxins are naturally occurring chemicals produced by algal or microbial organisms and are concentrated in contaminated seafood. All are heat stable toxins that are not destroyed by normal cooking. The toxins are not detectable by organoleptic means. Except for the scombroid toxins, the toxins accumulate in fish or shellfish through amplification in the food chain. The chemicals that cause Scombroid poisonings are produced by various bacteria on fish that have been thermally abused after harvest. The hazard posed by these toxins is dependant on dose, frequency of exposure, relative toxicity of the chemical and host factors. Many of these substances can serve as useful research tools or molecular models for the design of new drugs and pesticides. Substantial increases in seafood consumption in recent years, together with globalization of the seafood trade, have increased potential exposure to these agents. Marine toxins produce neurological, gastrointestinal, and cardiovascular syndromes, some of which result in high mortality and long-term morbidity.

Algal Toxins

Algae constitute most of the biomass of the oceans. Of ~5000 species of algae, ~40 species, of which most are dinoflagellates (*pyrrhophyta* division), produce potent toxins. These algae are a main source of food for shellfish and the larvae of crustaceans. Algae are also an important food source of small herbivorous fish, which may be consumed by larger fish that is in turn, eaten by humans. Under appropriate environmental conditions, algae can

reproduce with extraordinary rapidity, even to the point of discoloring the sea, producing algal blooms that include red tides. Toxin may be so concentrated in waters under these circumstances that it can be aerosolized by surf and cause a transient syndrome of inhalational intoxication in humans.

Paralytic shellfish poisoning: Paralytic shellfish poisoning is a severe disease with rapid onset that may be life threatening. The syndrome is exclusively neurological. The illness is caused by saxitoxin and closely related marine toxins. Saxitoxin is a water-soluble, heat-stable tetrahydropurine that is produced by certain dinoflagellates and possibly other algae and bacteria. The mode of action of saxitoxin is blockage of voltage-gated sodium channels in nerve and muscle cell membranes, blocking nerve signal transmission.

Diarrheic shellfish poisoning: Diarrheic shellfish poisoning is a rapid-onset, self-resolving illness with exclusively gastrointestinal symptoms. Symptoms are typically severe, but always self-limiting. The illness is caused by okadaic acid and possibly related toxins produced by certain dinoflagellates. Okadaic acid is a lipophilic polyether that inhibits eukaryotic protein phosphatases and is thought to cause diarrhea by phosphorylation of control proteins that result in sodium release by intestinal mucosal cells.

Amnesic shellfish poisoning: Amnesic shellfish poisoning is a rare illness with symptoms ranging from gastrointestinal disturbance to severe and unusual neurological manifestations. It is caused by domoic acid, a water-soluble, heat-stable amino acid that is produced by certain algal diatoms of *pseudo-nitzschia* species.

Ciguatera: Ciguatera is typically a self-limiting illness manifesting combinations of gastrointestinal, neurological, and cardiovascular symptoms. It is the one of the most common forms of seafood intoxication, with an estimated 20,000–50,000 cases occurring annually worldwide. Illness is caused by 2 dinoflagellate toxins. Ciguatoxin and closely related toxins are lipophilic, heat-stable polyethers that open voltage-sensitive sodium channels at the neuromuscular junction, resulting in membrane hyperexcitability, spontaneous repetitive neurotransmitter release, blockage of synaptic transmission, and depletion of synaptic vesicles.

Neurotoxic shellfish poisoning: Neurotoxic shellfish poisoning produces a transient illness characterized by gastrointestinal and neurological symptoms. Illness is caused by members of the brevetoxin family of toxins, which are lipophilic polyethers that, like ciguatera, open voltage-sensitive sodium channels.

OTHER TOXINS

Scombroid fish poisoning (histamine fish poisoning): Scombroid fish poisoning is probably the most common seafood-related intoxication and is mostly caused by consumption of fish with high histamine levels, and symptoms are essentially the same as those associated with histamine toxicity.

Puffer fish poisoning: Puffer fish poisoning is a lethal intoxication resulting from consumption of toxic species of the puffer fish, which is also known as fugu, globefish, or blowfish and which resides in shallow waters of tropical and temperate seas.

Drugs from mineral origin: Minerals that are essential to life are the source of metals and other inorganic elements involved in the most fundamental processes. These contain metals such as manganese, copper, zinc, and iron. The human skeleton is composed of calcium and phosphorus and traces of other ions, e.g. magnesium, sulfur, and sodium, embedded in an organic matrix. The regulation of body fluid volume and acid–base balance requires the cations sodium, potassium, magnesium, and calcium. The principal anion is chloride. Calcium also plays a role in neuromuscular

excitability and blood coagulation. Metabolic energy, cellular homeostasis, and most enzyme activities are dependent on phosphorus. The electron-transport chain requires copper and iron. Several vitamins (qv) contain sulfur; one contains cobalt. Hormones (qv) contain iodine, sulfur, and zinc. Some elements found in body tissues have no apparent physiological role, but have not been shown to be toxic. Examples are rubidium, strontium, titanium, niobium, germanium, and lanthanum. Other elements are toxic when found in greater than trace amounts, and sometimes in trace amounts. These latter elements include arsenic, mercury, lead, cadmium, silver, zirconium, beryllium, and thallium. The interactions of mineral nutrients with carbohydrates, fats, and proteins, minerals with vitamins (qv), and mineral nutrients with toxic elements are areas of active investigation. The amount of each element required in daily dietary intake varies with the individual bioavailability of the mineral nutrient. Bioavailability depends both on body need as determined by absorption and excretion patterns of the element and by general solubility, and on the absence of substances that may cause formation of insoluble products, e.g. calcium phosphate $Ca_3(PO_4)_2$. The essential mineral nutrients are classified either as principal elements or as trace and ultratrace elements.

The list of plant drugs derived from minerals are given below, a few of them have significance as pharmaceutical aids:

SHILAJIT

Synonyms: Vegetable asphalt, bitumen, asphaltum.

Origin: Shilajit literally means 'rock overpowering' and is a natural exudate from the rocks of the Himalayas and other mountainous regions of the world. According to *Sushruta*, in the months of May-June the sap or juice of plants comes out as gummy exudation from the rocks of mountains due to strong heat of sun and *Rasarangini*, *Dwarishtarang* also claim that the Shilajit is an exudation of latex gum-resin, etc. of plants which comes from the rocks of mountains in presence of scorching heat.

Constituents: Shilajit mainly consists of resins like benzoic acid, hippuric acid, fulvic acid, minerals like silica, iron, antimony, calcium, copper, lithium, magnesium, manganese, molybedenum, phosphorous, silica, sodium, strontium, zinc.

Biomedical action: It is a superb mineral supplement that benefits the kidneys, urinary and reproductive systems. It has diuretic activity, lithotriptic, anti-diabetic, nervine and tonic. It strengthens the whole reproductive system and is a tonic to the sex organs. It also benefits the female reproductive system where there is weakness, infertility, dysmenorrhoea.

TALC

Synonyms: Talcum, french talc and soap stone.

Origin: The mineral talc is a hydrous magnesium silicate. A massive talcose rock is called steatite, and an impure massive variety is known as soapstone.

Properties: Talc is used commercially because of its fragrance retention, luster, purity, softness, and whiteness. Commercially important properties of talc are its chemical inertness, high dielectric strength, high thermal conductivity, low electrical conductivity, and oil and grease adsorption. It is insoluble in water, weak acids and weak alkalies.

Composition: Talc is composed of layer of magnesium made of either oxygen or hydroxyl octahedral that lies sandwitched between two layers of siliconoxygen tetrahedron.

Uses: Talc is used in ceramics, paint, paper, and plastics. It is also used as dusting powder, pharmaceutical aid, as a filtration aid and ideal excipient as well as glidant.

ASBESTOS

Synonyms: Amianthus.

Origin: Asbestos is a naturally occurring mineral found in underground rock formations. It is recovered by mining and rock crushing. Asbestos is also mined in India, but quantity and quality-wise it is of no relevance to our asbestos cement production. There are two groups of asbestos: Serpentine and amphiboles.

- **Serpentine asbestos**, such as chrysotile, has curly-shaped fibres that can shear into smaller fibrils. Chrysotile fibres consist of aggregates of long, thin, flexible fibrils that resemble scrolls or cylinders of uniform chemical composition.
- **Amphiboles** crystallise in straight double chains resulting in needle-like structures. They tend to be more brittle.
- **Asbestos fibre**, (composed mainly of magnesium and silica), is a great reinforcing agent. Its tensile strength is greater than steel, it has other rare and highly valued fire retardant, chemical resistant and heat insulating qualities. In fact it is a magic mineral and no other substitute can match its properties.
- Six common forms of asbestos are known as actinolite, amosite, anthophyllite, chrysotile, crocidolite and tremolite.

Description: Asbestos refers to a number of naturally occurring mineral silicates. The macroscopic asbestos fibres are actually bundles of thinner fibres made up of fibrils. Each macroscopic fibre is highly anisotropic and tends to decompose into its thinner constituents under industrial handling.

Properties: Asbestos is neither volatile nor soluble, they can occur in suspension in both air and water. Large fibres are removed from air and water by gravitational settling at a rate which depends on their size. Small fibres can remain suspended for long periods of time. Interaction with natural organic matters may increase precipitation. Designates a group of naturally occurring fibrous serpentine or amphibole minerals that have extraordinary tensile strength, conduct heat poorly and are relatively resistant to chemical attack.

Uses: As insulation, cement, fireproof clothing, and brake linings. However, its use is declining.

KAOLIN

Synonyms: China clay, porcelain clay, bolus alba, terra alba, white bole or argilla.

Source: Kaolin is a plastic raw material, particularly consisting of the clay mineral kaolinite. The chemical formula is $Al_2O_3.2SiO_2.2H_2O$ (39.5% Al_2O_3, 46.5% SiO_2, 14.0% H_2O). It is formed by rock weathering.

Description: Kaolinite ranks among phyllosilicates, which are stratified clay minerals formed by a net of tetrahedral and octahedral layers.

Properties: Kaolinite has very little isomorphic substitution of Al for Si in the tetrahedral layer. Accordingly, it has a low cation exchange capacity. Kaolinite easily adsorbs water and forms a plastic, paste-like substance. Due to its adsorbent capability and lack of primary toxicity, kaolin is considered a simple and effective means to prevent or ameliorate the adverse effects exerted by many toxic agents.

Composition: Kaolin or China clay is a mixture of different minerals. Kaolin contains 10–95% of the mineral kaolinite and usually consists mainly of kaolinite (85–95%). Kaolinite is made up of tiny sheets of triclinic crystals with pseudohexagonal morphology. It also contains quartz and mica and also, less frequently, feldspar, illite, montmorillonite, ilmenite, anastase, haematite, bauxite, zircon, rutile, kyanite, silliminate, graphite, attapulgite, and halloysite.

Uses: Kaolin is used in face powders, liquid powders, powder creams, baby powders, compact rouge, face packs and in some

dentifrices. Clinically, *cataplasma kaolini* (kaolin, glycerin, boric acid, methyl salicylate, thymol and peppermint oil) was used in cases of deep-seated inflammation, carbuncles, septic wounds, etc. Kaolin possesses good covering power, good grease-resisting properties and adsorbs perspiration. Kaolin is a safe and dermatologically innocuous material that has a sedative and cooling effect on an inflamed and heated skin.

BENTONITE

Synonyms: Whilknite.

Source: Bentonite is a rock formed of highly colloidal and plastic clays composed mainly of montmorillonite, a clay mineral of the smectite group, and is produced by *in situ* devitrification of volcanic ash. Differences among brands depend on montmorillionite content and percentage of impurities such as sand. Sodium bentonites are the most popular types in the USA. Other countries often use calcium bentonite, which may have greater or lesser protein removal activity than sodium bentonite.

Composition: The principle constituents of bentoninte is montmorillonite. It may also contain feldspar, cristobalite, and crystalline quartz.

Properties: The special properties of bentonite are derived from the crystal structure of the smectite group, which is an octahedral alumina sheet between two tetrahedral silica sheets. It is an ability to form thixotrophic gels with water, an ability to absorb large quantities of water, and a high cation exchange capacity. A hydrated aluminum silicate, bentonite has a negative charge, reacting with positively charged particles such as proteins. In solution, it behaves like a series of small, absorbent plates.

Use: Bentonite is used in most cement slurries for decreasing slurry weight and increasing slurry volume. In bentonite cement diesel-oil (BCDO) and bentonite diesel-oil (BDO) slurries, bentonite forms a thick, paste-like material that helps prevent lost circulation.

CALAMINE

Synonyms: Prepared calamine.

Origin: Calamine is a mixture of zinc oxide (ZnO) with about 0.5% iron (III) oxide (Fe_2O_3). It is a mineral species consisting of zinc carbonate, $ZnCO_3$, and forming an important ore of zinc. It is rhombohedral in crystallization and isomorphous with calcite and chalybite.

Description: The color of the pure mineral is white; more often it is brownish, sometimes green or blue: A bright-yellow variety. The hardness is 5 and specific gravity is 4.4. It is insoluble in water but soluble in hydrochloric acid.

Composition: Contains zinc carbonate (99.9%) colored with iron (III) oxide. The pure material contains 52% of zinc, but this is often partly replaced isomorphously by small amounts of iron and manganese, traces of calcium and magnesium, and sometimes by copper or cadmium.

Uses: It is the main ingredient in calamine lotion and is used as an antipruritic (anti-itching agent) to treat mild pruritic conditions such as sunburn, eczema, rashes, poison ivy, chickenpox, insect bites and stings. It is also used as a mild antiseptic to prevent infections that can be caused by scratching the affected area, and an astringent to dry weeping or oozing blisters and acne abscesses.

KIESELGUHR

Synonyms: Diatomaceous earth, diatomite, diahydro, kieselguhr, kieselgur and celite.

Origin: It is a naturally occurring, soft siliceous sedimentary rock, that is easily crumbled into a fine white to off-white powder. Diatomaceous earth or Kieselguhr is composed of the siliceous shells of fossil diatoms (minute unicellular plants), or of the debris of fossil diatoms.

Description: It has a particle size ranging from less than 1 micron to more than 1 millimeter, but typically 10 to 200 microns. This powder has an abrasive feel, similar to pumice powder and is very light, due to its high porosity.

Composition: The typical chemical composition of oven dried diatomaceous earth is 80 to 90% silica, with 2 to 4% alumina (attributed mostly to clay minerals) and 0.5 to 2% iron oxide and consists of fossilized remains of diatoms, a type of hard-shelled algae.

Uses: It is used as a filtration aid, as a mild abrasive, as a mechanical insecticide, as an absorbent for liquids, as cat litter, and as a component of dynamite. As it is also heat-resistant, it can be used as a thermal insulator. Diatomite is also used as an insecticide, due to its physico-sorptive properties.

CONCLUSION

Herbal formulations mean a dosage form consisting of one or more herbs or processed herbs in specified quantities to provide specific nutritional, cosmetic benefits meant for use to diagnose, treat, mitigate diseases of human beings or animals, alter the structure or physiology of human beings or animals.

Rational phytotherapy is a modern concept of herbal medicines using, which are made of standardized herbal extracts. The quality of each final product is guaranteed by the use of raw materials of a standard quality, defined process of production, and validated equipment. Quality control of herbal drugs and herbal isolates according to the requirements of pharmacopoeia and other relevant regulations. The scope of phytopreparation quality control depends on its pharmaceutical form.

The formulation of a new phytopreparation is a process that has strictly defined phases: From analysis of literature and market, through defining recipes, validation of the production process, quality control of a final product to the preparation of technological and registration documents.

Herbal formulations contain an active substance or herbal substance or herbal preparation or herbal substance in combination with one or more herbal preparations. Herbal formulations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation include comminuted or powdered. Whole, fragmented or cut plants, plants parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh were used in the preparations of herbal formulations. Different herbal formulations are tinctures, extracts, essential oils, expressed juices and processed exudates. Markers are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purpose independent of whether they possess any therapeutic activity. Markers serve to calculate the quantity of herbal substance or herbal preparation in the herbal formulations if the markers have been quantitatively determined in the herbal substance or herbal preparations. Characterization of herbal formulations includes design and development, pharmacopoeial tests and acceptance criteria, periodic testing, release, shelf-life acceptance criteria, in-process tests.

CHAPTER 10

Bioavailability of Herbals

DEFINITION

According to the code of federal regulations, bioavailability is the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. In other words, bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action.

Oral bioavailability depends on a number of factors, primarily drug permeability, aqueous solubility, dissolution rate, pre-systemic metabolism, first-pass metabolism and susceptibility to efflux mechanisms. Among these factors low permeability and poor solubility stands as the most frequent causes of low oral bioavailability.

When drugs are administrated by intravenous route maximum bioavailability is achieved, whereas if administered orally they are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bioavailability. Many natural compounds from medicinal plants have capacity to enhance the bioavailability when co-administered with another drug.

A natural bioenhancer is an agent of herbal origin or any phytomolecule, which is capable of enhancing bioavailability and bioefficacy of a particular drug or nutrient with which it is combined, without any typical pharmacological activity of its own at the dose used. They tend to decrease the dose of active drug required for the optimal endpoint of the treatment strategy.

In other words, bioenhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug.

Bioenhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug. The need for bioenhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive Fig. 10.1.

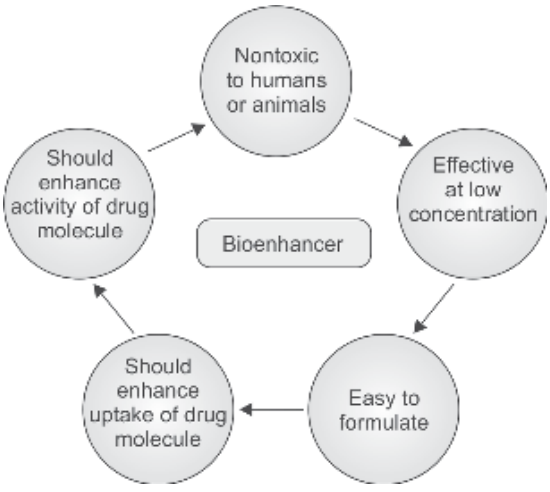

Nontoxic to humans or animals
Effective at low concentration
Easy to formulate
Should enhance uptake of drug molecule
Should enhance activity of drug molecule
Bioenhancer

Fig. 10.1: Ideal properties of bioenhancers

BIOENHANCERS

Advantages of Bioenhancers

1. Minimize drug toxicity and adverse reactions
2. Reduce toxicity
3. Shorten treatment period
4. Reduce drug resistance problems
5. Improve oral absorption of range of nutrients
6. Reduce dose
7. Due to dose economy treatment is cost economy
8. Effective in combination with various classes of drugs

Mechanisms of Action of Natural Bioenhancers (Fig. 10.2)

There are several mechanisms of action by which herbal bioenhancers work. Among the various mechanisms of action postulated for natural bioenhancers some are P-gp inhibition activity, reduction in acid secretion, increase in gastrointestinal blood supply, inhibition of gastrointestinal transit, gastric emptying, increase in intestinal motality, modifications in GIT epithelial cell membrane permeability and inhibition of first pass metabolism and metabolizing enzymes. Flavone, quercetin and genistein have showed a considerable P-gp inhibition activities. Additionally, naringin and sinomenine were also reported to be inhibitors for efflux transporters such as P-gp and breast cancer resistance protein. Many natural compounds are effective in improving the intestinal absorption of other drugs and nutrients, example of such agents are: Bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers. These surfactants act as bioenhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Trimethylated chitosan increase drug absorption by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions.

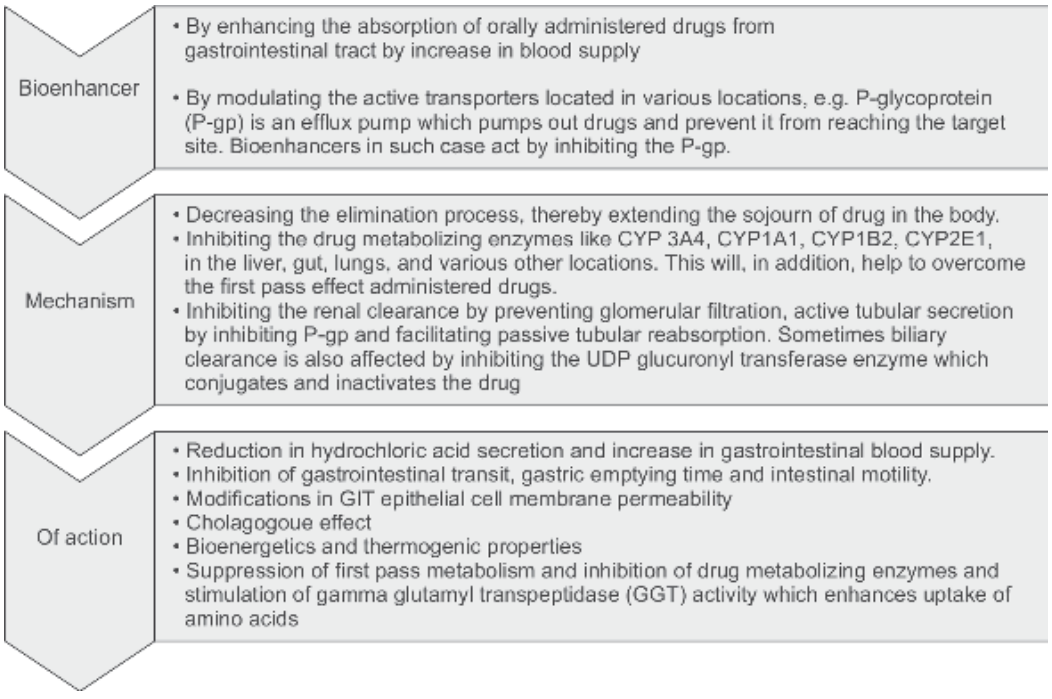

Bioenhancer
• By enhancing the absorption of orally administered drugs from gastrointestinal tract by increase in blood supply
• By modulating the active transporters located in various locations, e.g. P-glycoprotein (P-gp) is an efflux pump which pumps out drugs and prevent it from reaching the target site. Bioenhancers in such case act by inhibiting the P-gp.
Mechanism
• Decreasing the elimination process, thereby extending the sojourn of drug in the body.
• Inhibiting the drug metabolizing enzymes like CYP 3A4, CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs, and various other locations. This will, in addition, help to overcome the first pass effect administered drugs.
• Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting P-gp and facilitating passive tubular reabsorption. Sometimes biliary clearance is also affected by inhibiting the UDP glucuronyl transferase enzyme which conjugates and inactivates the drug
Of action
• Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.
• Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility.
• Modifications in GIT epithelial cell membrane permeability
• Cholagogoue effect
• Bioenergetics and thermogenic properties
• Suppression of first pass metabolism and inhibition of drug metabolizing enzymes and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids

Fig. 10.2: Mechanisms of action of natural bioenhancers

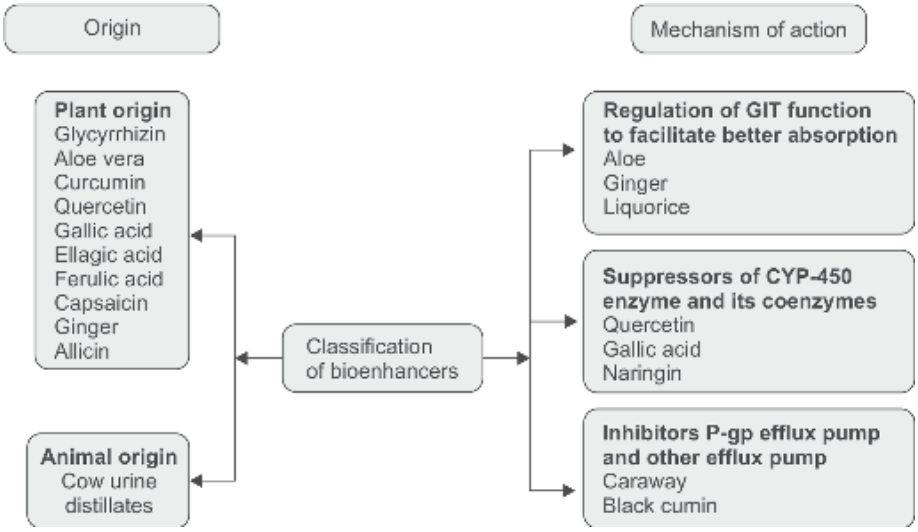


Fig. 10.3: Classification of bioenhancers

Classification of Bioenhancers (Fig. 10.3)

Bioenhancers can be classified based on their natural origin as well as based on the various mechanisms elicited by them when in combination with drugs to improve their bioavailability.

NATURAL PRODUCTS AS BIOENHANCERS

Piperine

Piperine (1-piperoyl piperidine) is a major amide alkaloid found in plants of *Piper nigrum* Linn. belonging to family Piperaceae. They are *Piper longum* (long pepper), *Piper nigrum* (black pepper). Piperine, or mixtures containing piperine, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs including vasicine, sparteine, sulfadiazine, rifampicin, phenytoin and propranolol. Piperine act by suppressing P-gp and cytochrome P450 enzymes, which counteract the metabolism of rifampicin via these proteins, thus enhancing the oral bioavailability of rifampicin. It also decreases the intestinal production of glucuronic acid, thus allowing more substances to enter the body in active form. It was found to increase the bioavailability of various drugs from 30% to 200%. The bioenhancing property of piperine was first utilized in the treatment of tuberculosis in human. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose from 450 to 200 mg. In human medicine piperine is approved to be combined with antitubercular drugs. Piperine also showed enhanced bioavailability when combined with nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infection. Piperine also increases the bioavailability of curcumin, the active principle of *Curcuma longa* (turmeric). A 20 mg dose of piperine can increase the bioavailability of curcumin by 20 fold in humans. Several animal studies on piperine have shown promising results in bioenhancing capacity of piperine for various drugs.

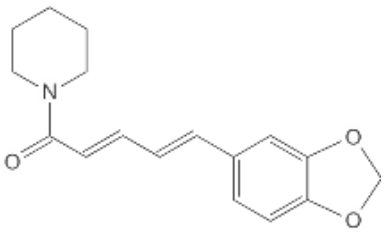


Fig. 10.4: Piperine

Black Cumin

Nigella sativa (black cumin) belonging to family ranunculaceae. It is extensively used in the Indian diasporas as spice, which may interact with co-administered drugs and affect their intestinal availability. In the *in vitro* study methanolic and hexane extracts of Nigella increased the permeation of amoxicillin significantly. In *in vivo* experiments black cumin enhanced amoxicillin bioavailability.

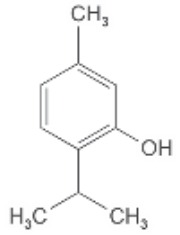


Fig. 10.5: Thymol

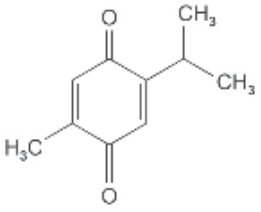


Fig. 10.6: Thymoquinone

Turmeric

Turmeric (*Curcuma longa*) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric, suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celiprolol and midazolam in rats. The bioenhancer nature of curcumin is similar to piperine. Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs.

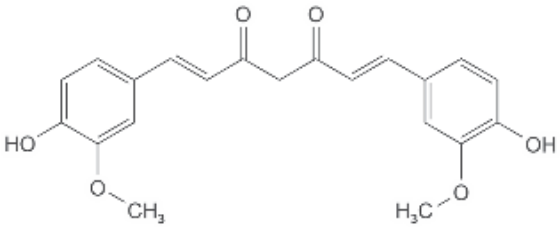


Fig. 10.7: Curcumin

Glycyrrhizin

Glycyrrhizin is a triterpenoid saponin found in *glycyrrhiza glabra* linn (leguminosae). The absorption-enhancing activity of sodium deoxycholate and dipotassium-glycyrrhizinate was much greater when coadministered with glycyrrhizin. The absorption enhancing activity of glycyrrhizin was increased by presence of other absorption enhancers. It enhances the transport of rifampicin, tetracycline, nalidixic acid, ampicillin and vitamin B1 and vitamin B12 across the gut membrane.

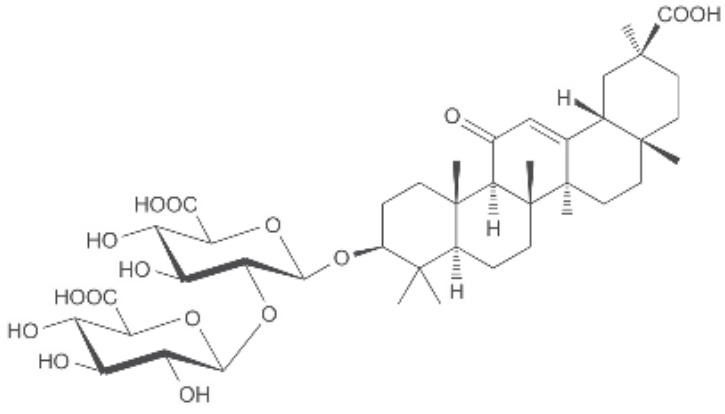


Fig. 10.8: Glycyrrhizin

Capsaicin

It is obtained from active component of *Capsicum annum* and other chilli species. It enhances the bioavailability of theophylline.

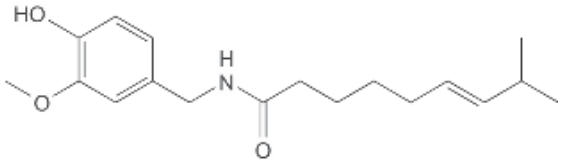


Fig. 10.9: Capsaicin

Cumin Oil

Cuminum cyminum Linn. (Apiaceae) is an annual herb, its fruits are generally used as spice. Cumin oils and its bioactive compound like luteolin seemed to attribute the bioavailability enhancing activity. Luteolin has been reported to be a potent P-gp inhibitor. Bioavailability enhancing activity of *C. cyminum* was revealed toward a number of drugs.

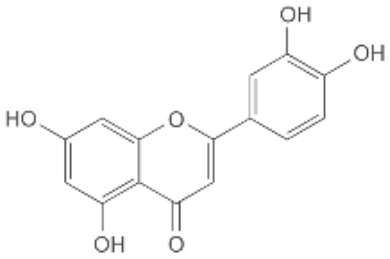


Fig. 10.10: Luteolin

Genistein

Genistein, well known as a phytoestrogen inhibits P-gp, breast cancer resistance protein (BCRP) and multidrug resistance associated protein 2 (MRP2) efflux function. The intestinal absorption of paclitaxel, a substrate for efflux transports such as P-gp, BCRP and MRP2 considerably increased when coadministered with genistein. It has been reported that the inhibition of the efflux transporters by genistein improve systemic exposure of paclitaxel.

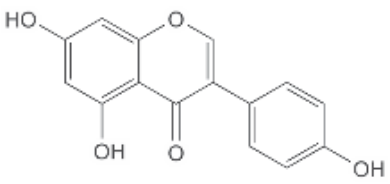


Fig. 10.11: Genistein

Naringin

Naringin is the major flavonoid glycoside found in grapefruits, that shows the inhibition of P-gp and CYP3A. It is capable of inhibiting intestinal CYP3A4, CYP3A1, CYP3A2. It has different pharmacological effects like anti-allergic, antioxidant, antiulcer and blood lipid lowering potential.

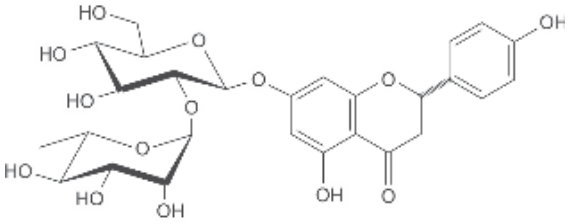


Fig. 10.12: Naringin

Sinomenine

Sinomenine, an alkaloid extracted from *Sinomenium acutum* (menispermaceae). Paeoniflorin, bioactive monoterpene glucoside has a poor bioavailability (3–4%) when administered orally. Co-administration of paeoniflorin with sinomenine, the AUC of paeoniflorin significantly increased, thus the oral bioavailability of paeoniflorin was enhanced by more than 12 times in rats treated with sinomenine.

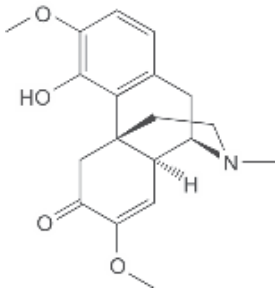


Fig. 10.13: Sinomenine

Quercetin

Quercetin is a flavonoid found in citrus fruits. It increases bioavailability, blood levels and efficacy of a number of drugs such as diltiazem, digoxin and epigallocatechin gallate. It possesses various pharmacological action as antioxidant, anti-inflammatory, anti-atherosclerotic activities. The mechanism of action of quercetin is inhibition of CYP3A4 and P-gp efflux pump.

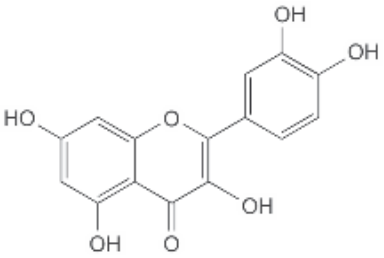


Fig. 10.14: Quercetin

Gallic Acid

Gallic acid is a trihydroxybenzoic acid, a type of phenolic acid, found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants. Possible mechanisms include competitive, non-competitive, uncompetitive, mixed or irreversible inhibition of CYP3A drug biotransformation. Gallic acid is proved to exert synergistic effect when administered with piperine and provides more therapeutic potential in reduced oxidative stress related complications.

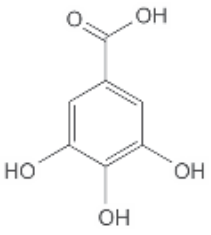


Fig. 10.15: Gallic acid

Peppermint Oil

Peppermint oil extracted from mentha species contains mainly menthol and menthone. Co-administration of cyclosporine and peppermint oil, it increased cyclosporine maximum concentration. It exerts its mechanism of action probably by CYP3A4 inhibition.

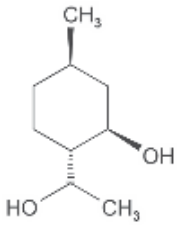


Fig. 10.16: Menthol

Nitrile Glycosides

Nitrile glycosides and its derivatives such as niazirin and niaziridin is obtained from the leaves, pods, and bark of *Moringa oleifera* (Moringaceae). These glycosides enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients.

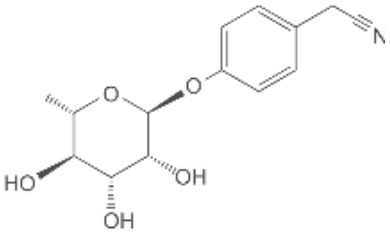


Fig. 10.17: Niazirin

Ginger

Zingiber officinale (zingiberaceae) possess significant bioavailability enhancement activity. Ginger mainly contains zingiberene, gingerol and shagol responsible for pungency of ginger. It has a powerful effect on mucous membrane of the gastrointestinal tract. It regulates the intestinal functions to facilitate absorption. Ginger when used in the dose of 10–30 mg/kg body weight acts as bio-

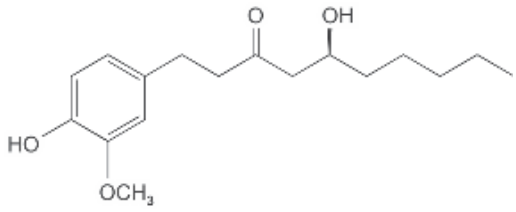


Fig. 10.18: Gingerol

enhancer. Pharmacological studies show that it dramatically enhanced the bioavailability of various medicines especially antibiotics such as amoxicillin, azithromycin, erythromycin, cephalexin, cefadroxil, and cloxacillin. Ginger acts powerfully on GIT mucous membrane.

Drumstick Pods

It contains niaziridin, a nitrile glycoside which is a powerful bioenhancer. It regulates GIT functions to facilitate better absorption. It enhances the bioavailability of rifampicin by 38.8 folds at 1.0 mg/ml. It also enhances the bioavailability of clotrimazole by 5–6 folds.

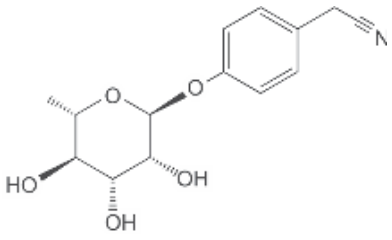


Fig. 10.19: Niaziridin

Allicin

It is obtained from *Allium sativum,* which is allyl sulphur compound. Allicin enhances fungicidal activity of amphotericin B against pathogenic fungi such as *Candida albicans*, *Aspergillus fumigatus* and yeast *Saccharomyces cerevisiae*.

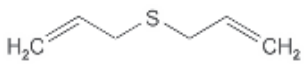


Fig. 10.20: Allyl sulfide

Caraway

Caraway is obtained from *Carum carvi*. Caraway seeds are carminative, mild stomachic, aromatic and diuretic actions. The caraway is proved to act as a bioenhancer and increases bioavailability of antibiotics, antifungal, antiviral and anticancerous drug. The dose range of bioactive fraction is in the range of 1–55 mg/kg body weight. It is more effective in combination with ginger (*Zingiber officinale*) and black pepper (piperine).

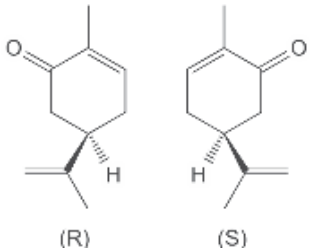


Fig. 10.21: Carvone

Stevia

Stevia is a natural sweetener and sugar substitute derived from the leaves of *Stevia rebaudiana.* The stevioside is the bioenhancing chemical constituent present in stevia. It enhances bioavailability of antitubercular, anti-leprotic, antifungal, anticancer and antiviral drugs. The effective dose is 0.01–50 mg/kg body weight.

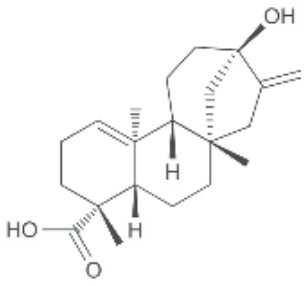


Fig. 10.22: Steviol

Table 10.1: Natural bioenhancers and their main mechanisms of action on various drugs

S. No.	Natural bioenhancer	Biological source	Mechanism of action
1.	Aloe	*Aloe vera*	Intercellular modulation
2.	Caraway	*Carum carvi*	Local mucosal tissue modulation
3.	Curcumin	*Curcuma longa*	Metabolism (UDP-glucuronyl transferase) inhibition
4.	Gallic acid ester	Gallnuts, tea leaves, oak bark	Metabolism (CYP3A) inhibition
5.	Genistein	*Pueraria lobata*	Efflux transporter (MRP) inhibition
6.	Gokhru extract	*Tribulus terrestris*	Local mucosal tissue modulation
7.	Grapefruit juice	*Citrus paradisi*	Efflux transporter (P-gp, MRP2); metabolism (CYP3A4) inhibition; renal uptake transporter (OATP) inhibition
8.	Lycopene	(Carotenoid) plant (red fruits and vegetables)	Dual carotenoid/LDL receptor mechanism for targeted hepatic delivery
9.	Peppermint oil (herbal) plant (peppermint)	*Mentha pipertita*	Metabolism (CYP3A) inhibition
10.	Piperine (alkaloid)	*Piper longum* and *piper nigrum*	Local mucosal tissue modulation; thermogenic activity
11.	Quercetin (flavonoid) plant	Citrus fruits, vegetables, leaves, grains	Efflux transporter (P-gp) inhibition

CONCLUSION

Herbal bioenhancers play a crucial role in enhancing the bioavailability and bioefficacy of different classes of drugs, such as antihypertensives, anticancer, antiviral, antitubercular and antifungal drugs at low doses.

Bioenhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug. The need for bioenhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive. Bioenhancers can be classified based on their natural origin as well as based on the various mechanisms elicited by them when in combination with drugs to improve their bioavailability.

Herbal bioenhancer is phyto-molecules that at low doses promote and augment the bioavailability or biological activity of drug. Bioenhancers are such agents, which by themselves are not therapeutic entities but when combined with an active constituent proceed to the potentiating of the pharmacological effect of the drug. Such formulations have been found to increase the bioavailability or bioefficacy of a number of drugs even when reduced doses of drugs are present in such formulations.

CHAPTER 11

Pharmacovigilance of Herbal Medicines

DEFINITION

The word "pharmacovigilance" is derived from *pharmakon* (drug in Greek) and *vigilare* (keep an eye on/monitor in Latin). It is well-defined as the science and activities relating to the detection, assessment, and prevention of adverse drug reactions in humans. Pharmacovigilance is an important and integral part of clinical research has been regarded as a type of continual monitoring of unwanted effects and other safety-related aspects of drugs, which are already placed in markets. It is also related to collection of information on the undesired effects of medications including herbal and traditional drugs from healthcare professionals and consumers. To be very precise study mainly focuses on observing and assessing ADRs (adverse drug reactions). The study is designed to continuously observe drugs for assessment of safety profile after approval and commercialization.

CONTRIBUTION OF PHARMACOVIGILANCE

- It contributes mainly towards the safety of drugs, initial identification of signs leading to the establishment of hypotheses and additional investigation through observational studies.
- Pharmacovigilance is the science devoted to decreasing the hazard of drug-related troubles to the consumers. It refers to the procedure of recognizing side effects of drugs, their treatment, documentation, reporting, and regulatory decisions.
- The overall study is deals with identification of side effects, hazards and adverse effects associated with pharmaceutical products and with minimizing the risk of any impairment that might come to patients.

World Health Organization (WHO), FDA (US Food and Drug Administration) and European Medicines Agency (EMA) announced regulation on pharmacovigilance to endorse

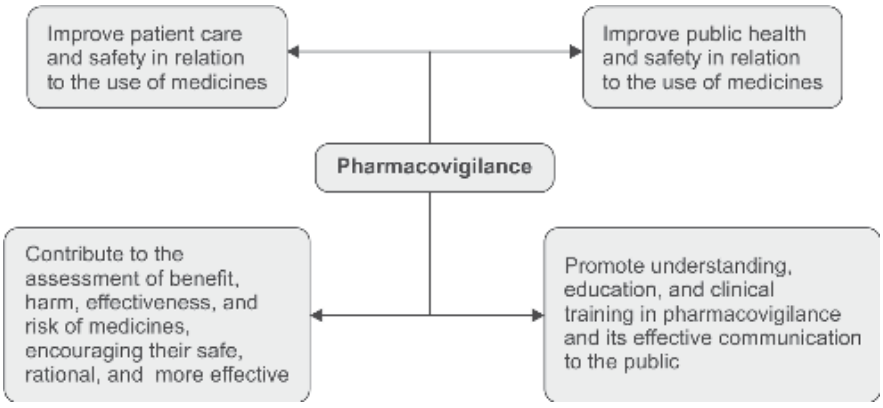

Improve patient care and safety in relation to the use of medicines
Improve public health and safety in relation to the use of medicines
Pharmacovigilance
Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational, and more effective
Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public

Fig. 11.1: Aims of pharmacovigilance

• Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
• Improve public health and safety in relation to the use of medicines.
• Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.
• Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational, and more effective (including cost-effective) use
Aims of pharmacovigilance
Aims of pharmacovigilance
Aims of pharmacovigilance

Fig. 11.2: Aims of pharmacovigilance

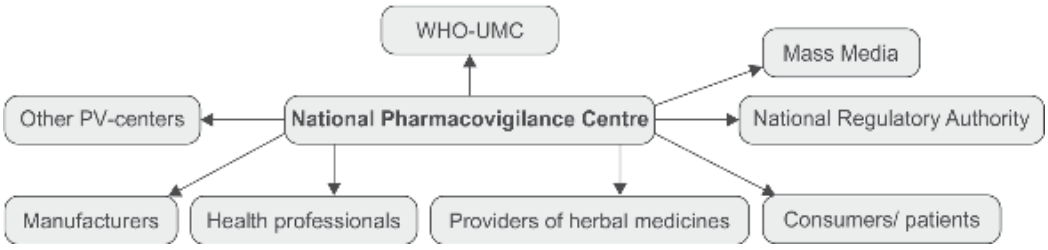


Fig. 11.3: Communication network of pharmacovigilance (PV)

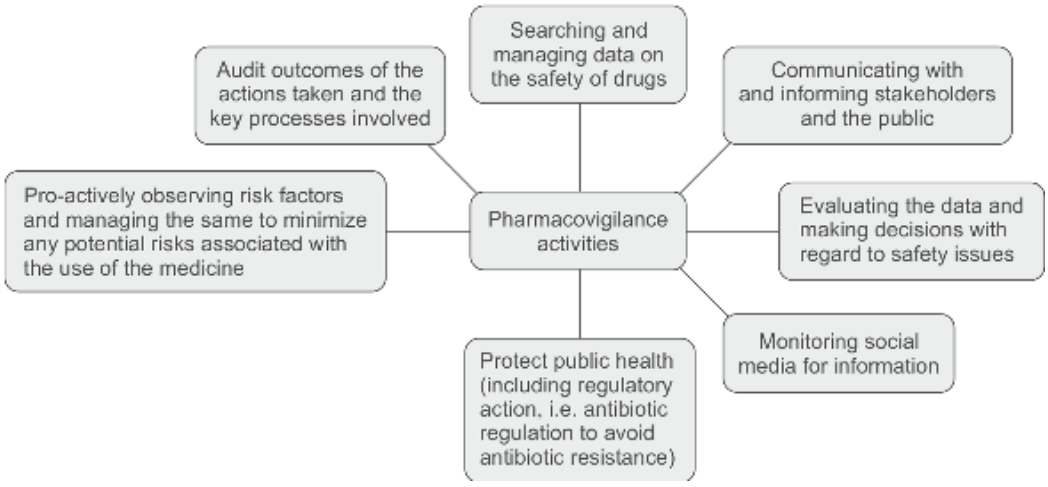

Searching and managing data on the safety of drugs
Audit outcomes of the actions taken and the key processes involved
Communicating with and informing stakeholders and the public
Pro-actively observing risk factors and managing the same to minimize any potential risks associated with the use of the medicine
Pharmacovigilance activities
Evaluating the data and making decisions with regard to safety issues
Monitoring social media for information
Protect public health (including regulatory action, i.e. antibiotic regulation to avoid antibiotic resistance)

Fig. 11.4: Pharmacovigilance activities

Unit-V

good vigilance practice standards with better transparency of pharmacovigilance data; thus paving the method for pharmacoepidemiological studies.

OBJECTIVES

1. The main objective of pharmacovigilance is to escalate spontaneous reporting of adverse drug reactions, i.e. reporting of suspecting adverse drug reactions by the medical stuff to a national coordinating center.
2. Other objectives involve demonstrating the effectiveness of drugs by observing their adverse effect profile for many years from the laboratory to the pharmacy; tracking any severe effects of drugs educating public

health and wellbeing in relation to the use of medicines; promising the safe, rational and cost-effective use of drugs; promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the generic public.

3. In addition, providing information to consumers, practitioners and regulators on the effective use of drugs along with designing programs and procedures for collecting and analyzing reports from patients and clinicians.

NEEDS

1. It is widely known that clinical development of medicines is a complex process which also includes herbal drugs and their products. Once a drug is marketed, it leaves the secure and protected scientific environment of clinical trials and is free for consumption by the general public. At this point, most herbal medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals.
2. Hence, need of pharmacovigilance in herbal drugs arises which include, securing the early detection of new adverse reactions or patients subgroups of exceptional sensitivity; and introducing certain measures in order to manage such risks.
3. Moreover, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions after being marketed.
4. Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs.
5. In order to provide consistency in the naming of herbs in adverse reaction (AR) reports, the WHO collaborating centre for international drug monitoring has recommended the use of proper scientific binomial names for herbs used in medicine, including the use of such names (where this information is available) in the coding of AR reports. This would ensure comparability between reports from various international pharmacovigilance databases.

ADVERSE DRUG REACTION (ADR) OF HERBAL MEDICINES

"That even a strong poison can become an excellent medicine if administered properly. On the other hand, even the most useful drug can act as a poison if handled carelessly."

—Charak

An adverse drug reaction is well-defined as a noxious and unintended response to a marketed health product, which occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function. It is well-known fact that plants play a significant role in the advancement of current medicines. More than 60–70% of modern medicines in the world market are directly or indirectly derived from plant products.

The herbal drugs like Ephedra products can produce toxicity in human beings with various

Table 11.1: List of herbs with suspected or known adverse effects

Herbal drug	Adverse effects
Aristolochia sp.	Kidney toxicity, carcinogenicity
St. John's wort	Gastrointestinal disturbances, allergic, reactions, fatigue, dizziness, confusion, dry mouth, photosensitivity
Ephedra	Hypertension, insomnia, arrhythmia, nervousness, tremor, headache, seizure, cerebrovascular event, myocardial infarction, kidney stones
Ginkgo biloba	Bleeding
Kava	Sedation, oral and lingual dyskinesia, torticollis, oculogyric crisis, exacerbation of Parkinson's disease, painful twisting movements of the trunk, rash

adverse effects like hepatic and renal problems. Due to the absence of clinical trials for most herbal medicinal products, post-marketing pharmacovigilance becomes a critical source of safety information. However, the assessment of adverse reactions associated with herbal medicinal products offers unique challenges in the quantity and quality of available information.

PREVENTION OF ADVERSE REACTIONS TO HERBAL MEDICINES

The achievement of pharmacovigilance system is capacity to avoid adverse reactions by understanding and using the necessary information collected. With ayurvedic medicines, the challenges would be at multiple levels.

1. Communication between the practitioners and policymakers of orthodox Western medicine and traditional Indian medicine is not adequate. Herbal practitioners are not aware of the need to report and where to report.
2. Patients are not adequately aware that herbal medicines can cause adverse reactions and can take medicines for years on end with no monitoring as they believe that these medicines can do no harm. Hence, they do not even give a history of taking these medicines.

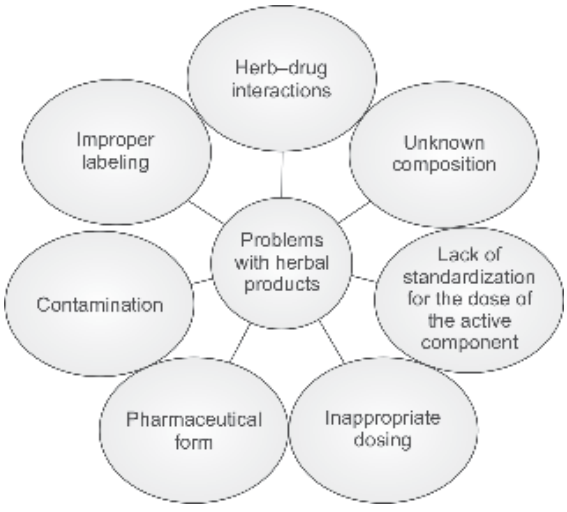


Fig. 11.5: Problems with the herbal products

3. Education in herbal or modern medicine at both undergraduate and postgraduate levels does not cover pharmacovigilance of herbal medicines, thus never exposing the young physicians to this concept.
4. The herbal pharmaceutical industry is not motivated to focus on pharmacovigilance of herbal medicines. Hence, there is no attempt at generating safety data—either before or after marketing of the formulation.

CHALLENGES OF PHARMACOVIGILANCE FOR TRADITIONAL MEDICINE PRODUCT

2,1 Complexity of herbal product:

1. **Lack of clinical trial data:** Unlike conventional medicines, systematic clinical trial data for many herbal and traditional medicine products is not always available. A license can be issued based on the history of medicinal use. It is difficult to obtain safety and efficacy data on the herbal product.
2. **Chemical complexity:** Herbal and traditional medicine remedies and preparations are chemically rich complex mixtures comprising several hundreds of constituents. The effects are likely to be attributed to a group of related constituents rather than a single constituent.
3. **Non-uniformity (products not standardized):** The profile of constituents is often not uniform throughout a plant and certain parts of the plant can be toxic. The precise profile of constituents is likely to vary between different batches of herbal materials, and factors such as environment, time of harvesting, storage, processing and drying can affect their variability. This makes it difficult to determine pharmacokinetics, pharmacodynamics and toxicology, and to establish which ingredient causes a safety concern.
4. **Quality assurance and control:** Unlike conventional pharmaceutical products, herbal and traditional medicines are prepared from materials of herbal origin which are often obtained from various geographical and commercial sources,

resulting in uncertain condition. Furthermore, procedures and techniques used in its manufacturing and quality control measure are often very different from those used for conventional medicines.

5. Lack of technical expertise and facilities and manpower to analyse the problem, particularly in identifying substandard, adulterated and contaminated, wrong medicinal plants, which is a common problem with traditional medicine products.

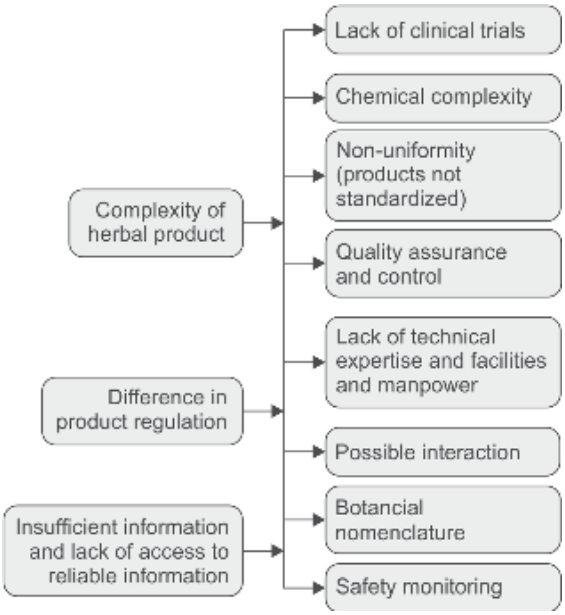

Lack of clinical trials
Chemical complexity
Non-uniformity (products not standardized)
Complexity of herbal product
Quality assurance and control
Lack of technical expertise and facilities and manpower
Difference in product regulation
Possible interaction
Botancial nomenclature
Insufficient information and lack of access to reliable information
Safety monitoring

Fig. 11.6: Challenges of pharmacovigilance for traditional medicine product

6. Possible interaction between different traditional medicine products and with allopathic medicines and foodstuffs.

PHARMACOVIGILANCE AND WHO DRUG MONITORING PROGRAM

Drug safety and pharmacovigilance is a vibrant and dynamic clinical and scientific discipline. Pharmacovigilance plays a vibrant role in providing necessary information about drug to choose it for treatment ensuring doctors, and patient for choosing a drug for treatment.

According to the information countries adverse drug reactions (ADRs) lead to mortality. In order to prevent or to reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital.

Pharmacovigilance programs in decade will describe in brief the possible consequences and evolution of the science. These eras the study is facing lots of challenges to progress improved health care systems in this worldwide pitch. Major challenges are globalization, web-based sales and information, broader safety concerns, public health versus pharmaceutical industry economic growth, monitoring of established products, developing and emerging countries, attitudes and perceptions to benefit and harm, outcomes and impact.

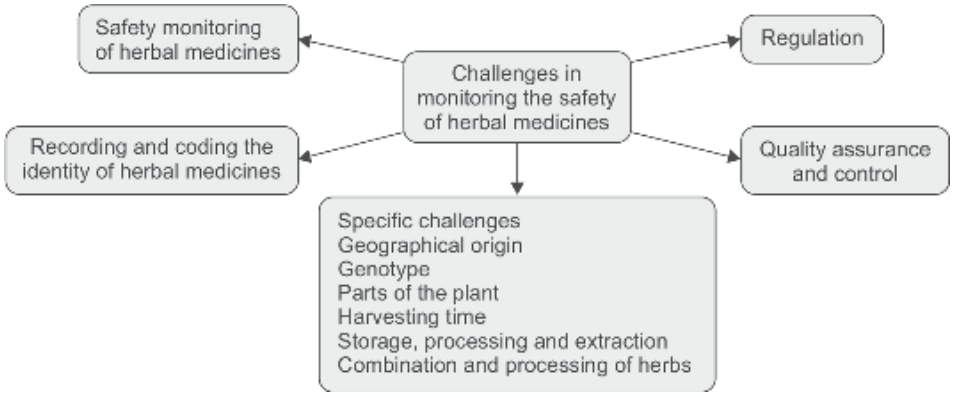


Fig. 11.7: Challenges in monitoring the safety of herbal medicines

The main concerns are pharmacovigilance is the science and activities relating to recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices, vaccines.

THE WHO INTERNATIONAL DRUG MONITORING PROGRAM

Under WHO international drug monitoring program centers of national pharmacovigilance are nominated by the competent authorities are accountable for the collection, processing, and evaluation of case reports of suspected adverse reactions supplied by healthcare professionals (mainly spontaneous reporting by physicians of reactions associated with the use of prescribed medicines).

The program presently encompasses a system of <70 national pharmacovigilance centers that function self-sufficiently, but whose purposes are synchronized and aided by the WHO and the UMC (Uppsala Monitoring Centre). The UMC manages the worldwide WHO data bank to which all case information acknowledged by the national pharmacovigilance centers. The UMC uses the database to recognize/notice signals of new adverse reactions from the cumulative data and to connect risk assessments back to the national pharmacovigilance centers and to others concerned with drug safety.

HISTORICAL PERSPECTIVES OF WHO DRUG SAFETY MONITORING

- In 2002, <sixty-five countries have their own and personal pharmacovigilance centers.
- Membership of the WHO for international drug monitoring is coordinated by the WHO collaborating centre known as the Uppsala Monitoring Centre (UMC).
- Pharmacovigilance is now based on complete scientific principles and is integral to effective clinical practice.
- The discipline needs to develop further to meet public expectations and the demands of modern public health.
- The sixteenth World Health Assembly agreed a resolution (WHA 16.36) that confirmed the necessity for initial act in respect to rapid distribution of statistics and information on adverse drug reactions and leads to formation of the WHO pilot research project for international drug monitoring.
- The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines.

WORLDWIDE SOLDIERS OF PHARMACOVIGILANCE

A multifaceted and vibrant association subsists between varied ranges of associates in the practice of drug safety monitoring. These associates must jointly anticipate, comprehend and respond to the repeatedly increasing demands and prospects of the public, health administrators, policy officials, politicians and health professionals.

PHARMACOVIGILANCE IN DRUG REGULATION

Pharmacovigilance programs and agendas made strong links with regulators and they understood that it plays a major role in confirming safety of medicinal products.

Clinical trial regulation: In developed and developing countries there is a substantial intensification in numbers of clinical trials. While approval of trials, regulatory bodies are involved in safety and efficacy of new products under investigation. Safety monitoring of medicines is an essential part of clinical practice.

The various factors which can enhance effective patient care are:

1. Education and training of health professionals in medicine safety.
2. Exchange of information between national pharmacovigilance centers and coordination of such exchange.
3. The linking of clinical experience of medicine safety with research and health policy.

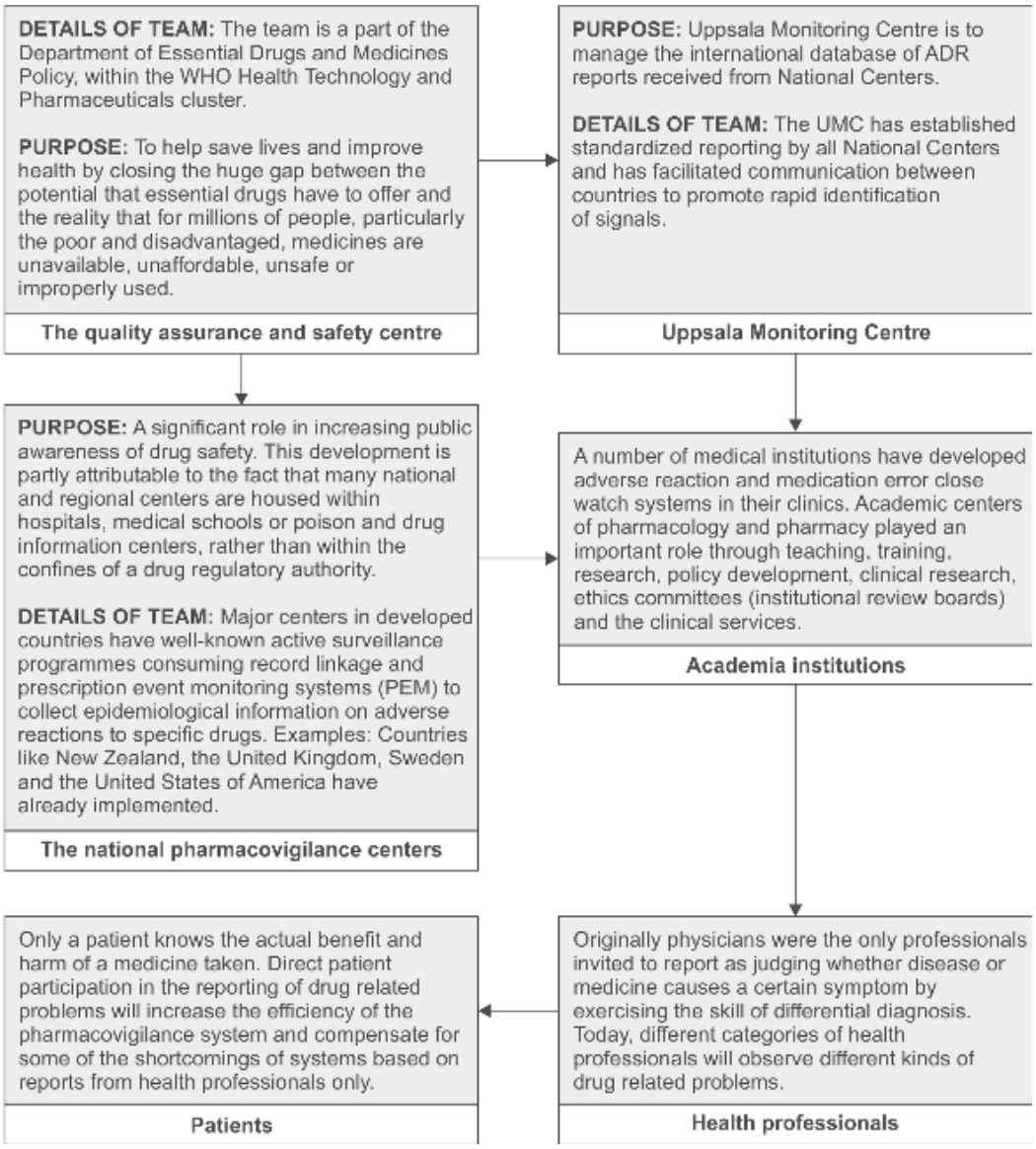

DETAILS OF TEAM: The team is a part of the Department of Essential Drugs and Medicines Policy, within the WHO Health Technology and Pharmaceuticals cluster.
PURPOSE: To help save lives and improve health by closing the huge gap between the potential that essential drugs have to offer and the reality that for millions of people, particularly the poor and disadvantaged, medicines are unavailable, unaffordable, unsafe or improperly used.
The quality assurance and safety centre
PURPOSE: Uppsala Monitoring Centre is to manage the international database of ADR reports received from National Centers.
DETAILS OF TEAM: The UMC has established standardized reporting by all National Centers and has facilitated communication between countries to promote rapid identification of signals.
Uppsala Monitoring Centre
PURPOSE: A significant role in increasing public awareness of drug safety. This development is partly attributable to the fact that many national and regional centers are housed within hospitals, medical schools or poison and drug information centers, rather than within the confines of a drug regulatory authority.
DETAILS OF TEAM: Major centers in developed countries have well-known active surveillance programmes consuming record linkage and prescription event monitoring systems (PEM) to collect epidemiological information on adverse reactions to specific drugs. Examples: Countries like New Zealand, the United Kingdom, Sweden and the United States of America have already implemented.
The national pharmacovigilance centers
A number of medical institutions have developed adverse reaction and medication error close watch systems in their clinics. Academic centers of pharmacology and pharmacy played an important role through teaching, training, research, policy development, clinical research, ethics committees (institutional review boards) and the clinical services.
Academia Institutions
Only a patient knows the actual benefit and harm of a medicine taken. Direct patient participation in the reporting of drug related problems will increase the efficiency of the pharmacovigilance system and compensate for some of the shortcomings of systems based on reports from health professionals only.
Patients
Originally physicians were the only professionals invited to report as judging whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis. Today, different categories of health professionals will observe different kinds of drug related problems.
Health professionals

Fig. 11.8: Worldwide soldiers of pharmacovigilance

Postmarketing safety drug monitoring: These comprise of detection of drug interactions, measuring the environmental burden of medicines used in large populations, assessing the contribution of 'inactive' ingredients to the safety profile, systems for comparing safety profiles of similar medicines, surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

Pharmacovigilance in national drug policy: The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. The education on rational use of medicines and pharmacotherapy monitoring result in multidisciplinary collaboration between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities,

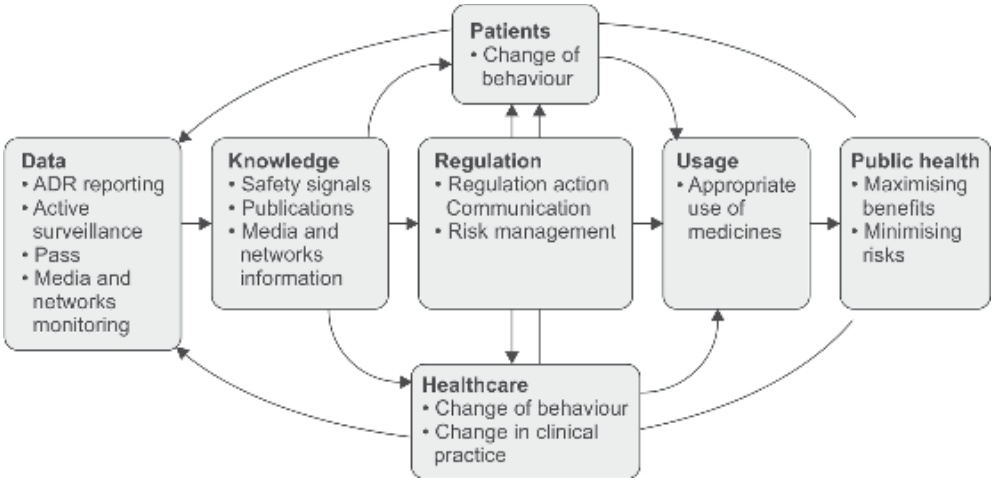


Fig. 11.9: Pathways and effects of pharmacovigilance activities

nongovernmental organizations (NGOs) and those professional associations.

Pharmacovigilance in disease control public health programmes: The monitoring of medicine safety in countries where there is no regulatory or safety monitoring system in place, or in remote areas with a little or no health care surveillance or infrastructure, has been identified as a matter for concern. The problems are especially apparent in situations that involve the use of medicines in specific communities. For example, for the treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis, and for the treatment of HIV/AIDS and tuberculosis. Pharmacovigilance should be a priority for every country with a public health disease control programs.

PHARMACOVIGILANCE AND INTERNATIONAL HEALTH

The current global network of pharmacovigilance centers is coordinated by the Uppsala Monitoring Centre would consider contentious and important drug safety issues that have the potential to affect public health adversely beyond national boundaries.

The Erice declaration provides a framework of values and practice for collection, analysis and subsequent communication of drug safety issues. The declaration urges governments and others involved in determining policies relating to the benefit, harm, effectiveness and risk of medicines to account for what they communicate to the public and patients. The declaration represented significant progress about changes for pharmacovigilance.

A worldwide master key for drug safety monitoring declaration challenges all the players like public health administration, health professionals, the pharmaceutical industry, government, drug regulators, the media, consumers to strive towards the highest ethical, professional and scientific standards in protecting and promoting safe use of medicines.

With this information patient feel more able to make their own therapeutic decisions, without assistance from doctor or pharmacist. The result has been increasing self-medication, licit and illicit sale of medicines over the Internet, and over-prescribing by doctors on patients' demand. This has had considerable effect on increased prescribing. Such public health programmes, however, need not focus only on patients but could be used for the benefit of the general public as well. Such awareness building and educational initiatives should also include children and elderly populations and could be greatly facilitated through partnerships with the media, educa-

tional institutions, governmental and non-governmental organizations.

The success of WHO international drug monitoring programmes is entirely dependent on the contributions of national pharmacovigilance centers. Ideally every country should have a pharmacovigilance center.

Challenges for the Erice declaration: There are several challenges facing pharmacovigilance programmes in achieving the aspirations of the Erice declaration. Like difficulties and risks in communicating conflicting or contentious messages to the public. For instance, during the course of immunization programmes, communication of new safety concerns associated with the vaccine(s) or with programmatic errors may result in a dramatic fall in coverage. Nonetheless, an approach of secrecy in such circumstances is likely to erode public trust and confidence, and it fails to respect the rights of the public to participate in decision-making. Not only do facts and figures need to be shared with the public, but also the process by which the data is assessed and how decisions are made should be shared openly. Another challenge is communication between national drug regulatory authorities and national pharmacovigilance centers needs to be improved so that regulatory decisions with possible international implications are rapidly communicated to regulators, to avoid widespread public concern or panic.

CONCLUSION

Pharmacovigilance continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines, all of which carry an inevitable and sometimes unpredictable potential for harm. When adverse effects and toxicity do appear, especially when previously unknown, it is essential that these are reported, analyzed and their significance is communicated effectively to the audience having knowledge to interpret the information. For all medicines, there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made.

To achieve this is to serve public health, and to foster a sense of trust among patients in the medicines they use that would extend the confidence in the health service in general, ensure that risks in drug use are anticipated and managed, provide regulators with the necessary information to amend the recommendations on the use of the medicines, improve communication between the health professionals and the public and educate health professionals to understand the effectiveness or risk of medicines that they prescribe.

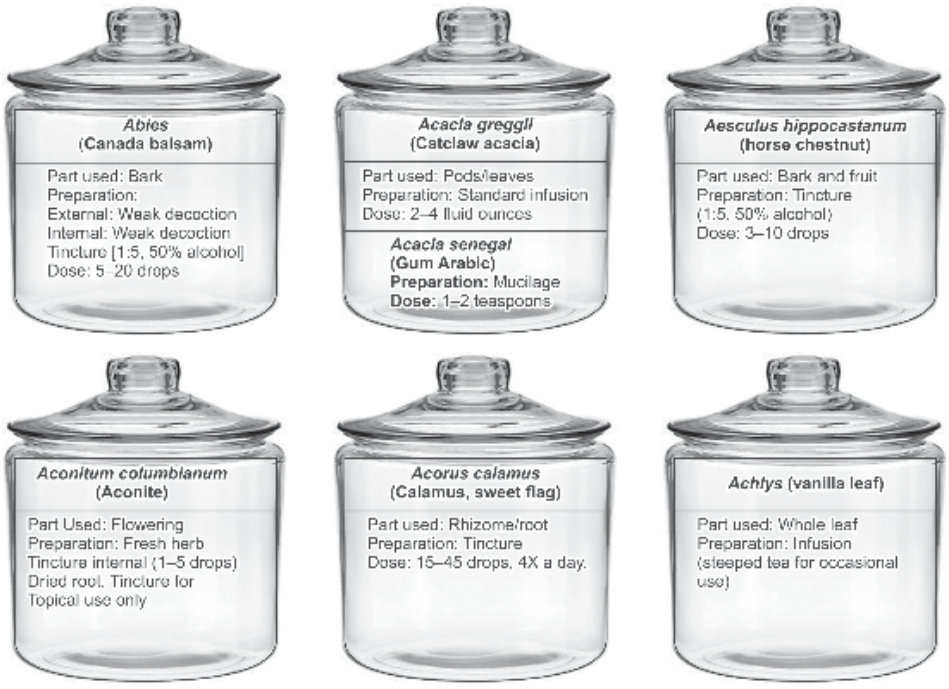
Unit VI

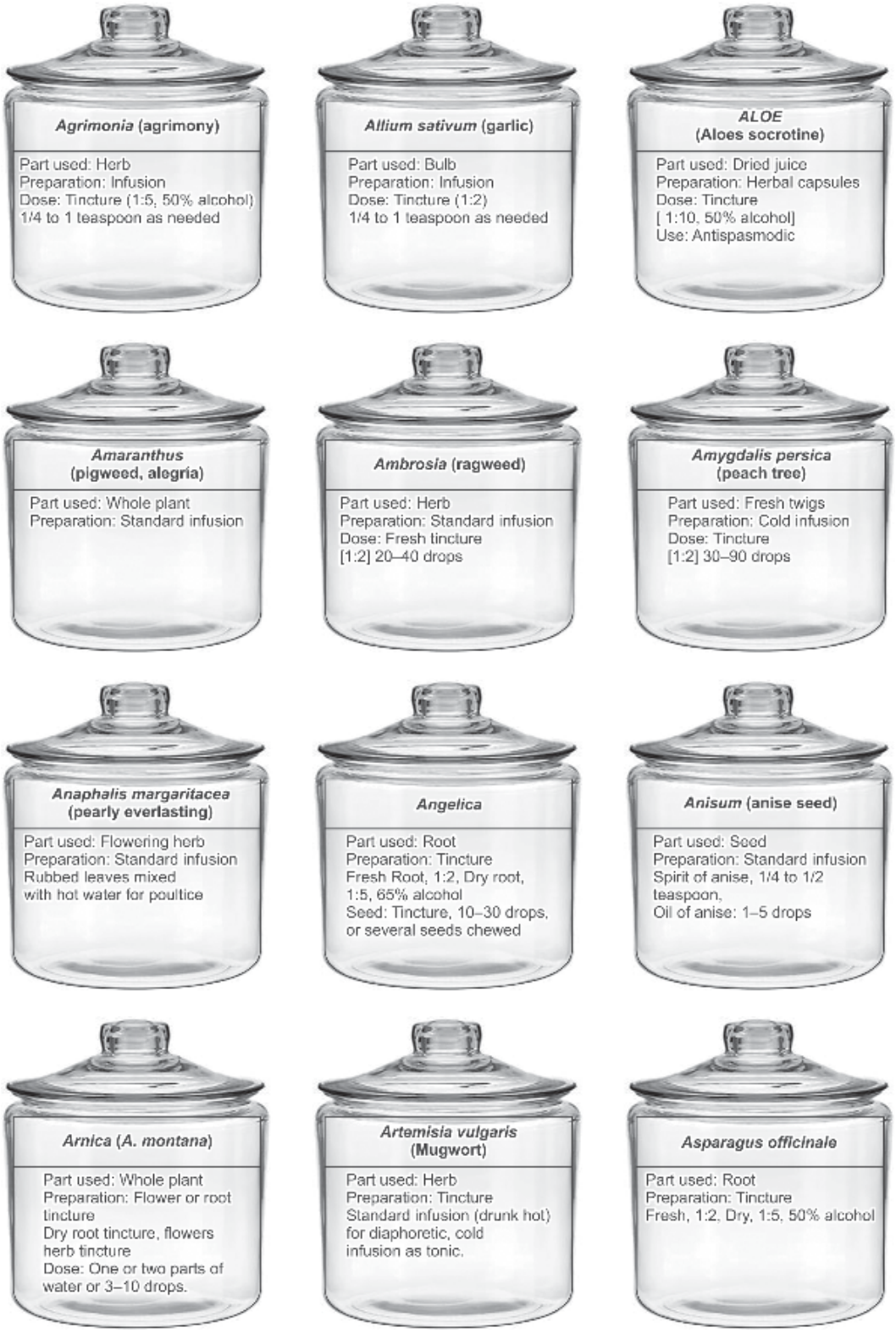
Traditional Medicinal Remedies

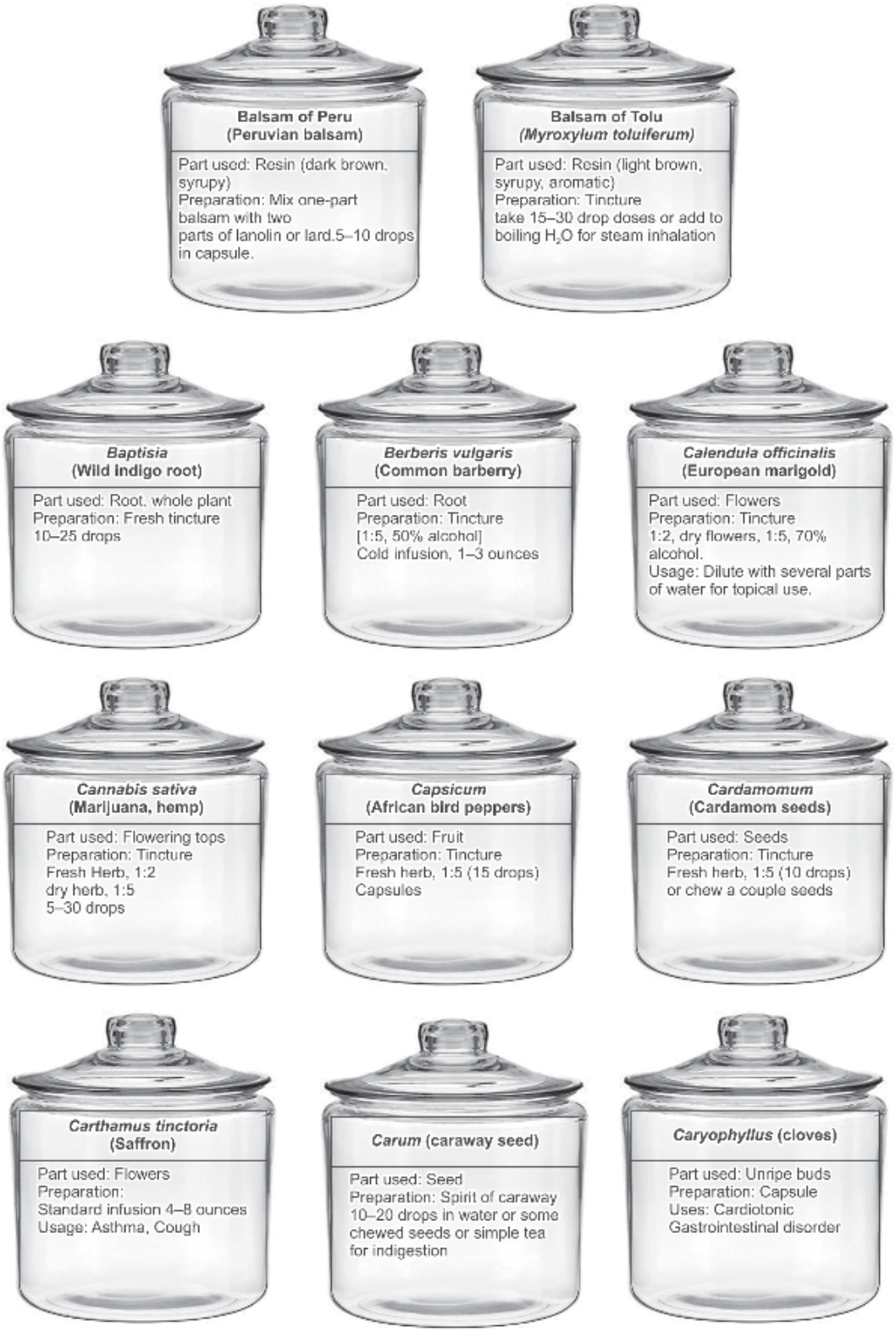
CHAPTER **12**

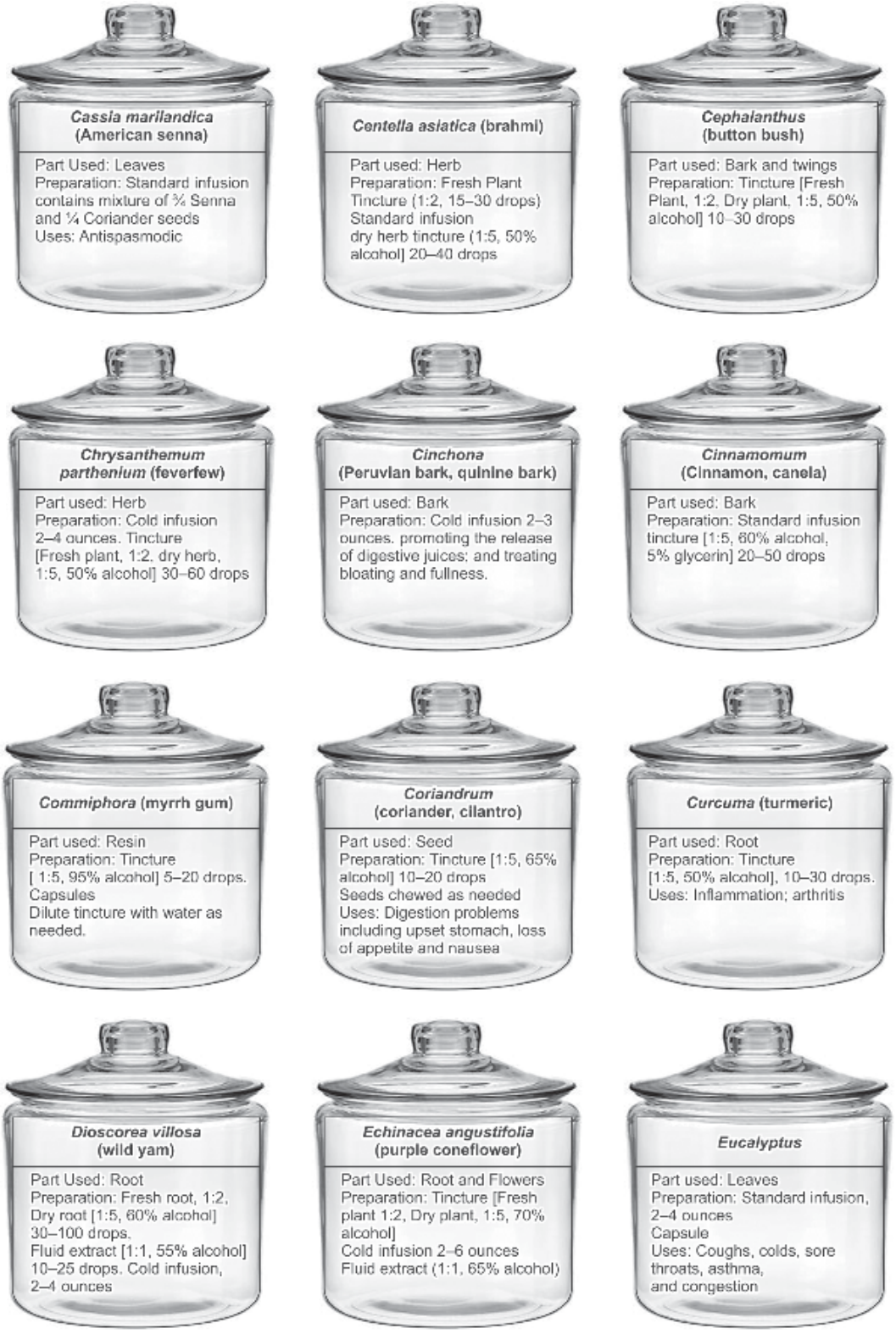
Frameworks of Major Botanical Medicines, with the Preferred Forms and Methods of their Preparations, Strengths, and Usage with Organ System Energetics

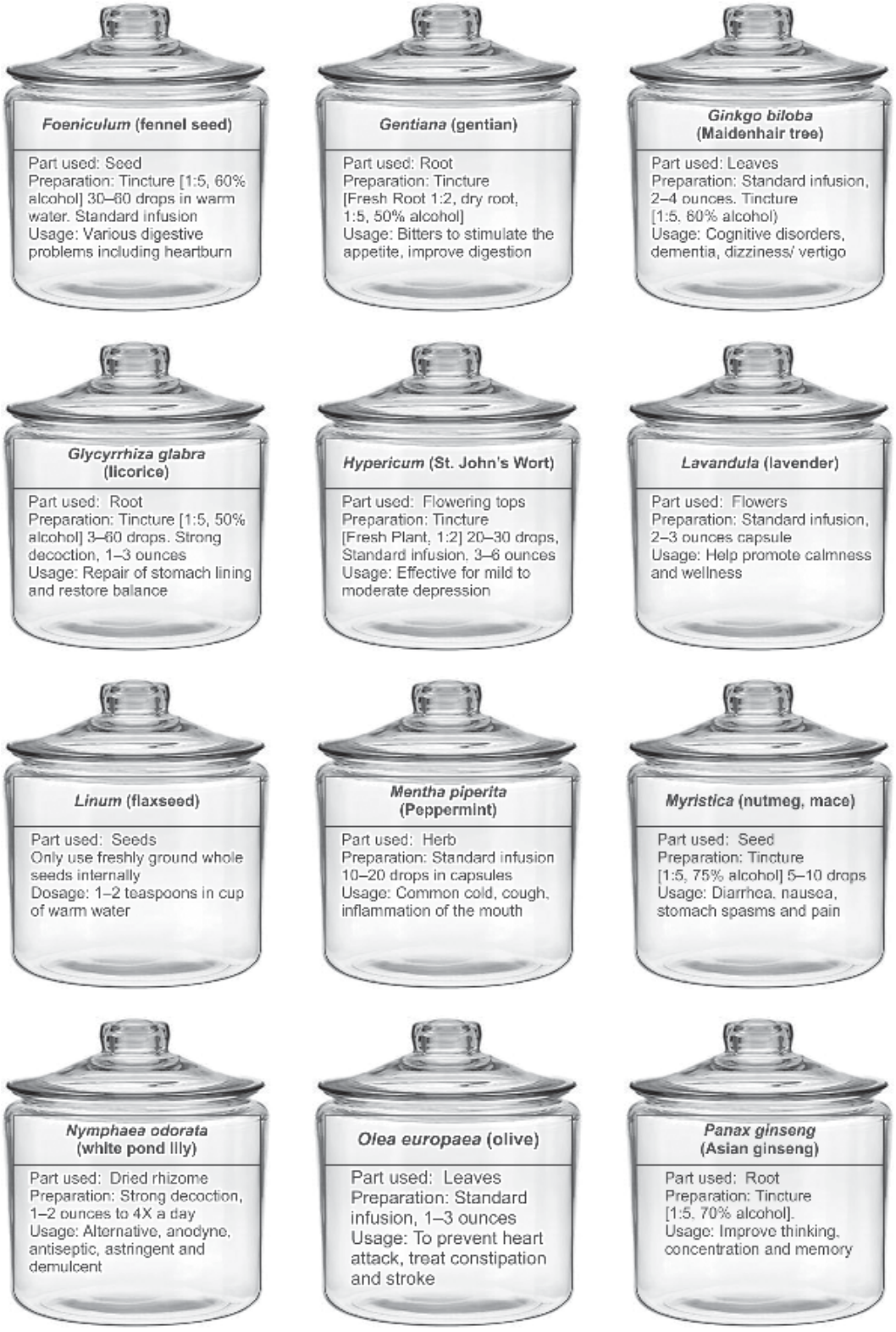
LIST OF MAJOR BOTANICAL MEDICINES, WITH THE PREFERRED FORMS AND METHODS OF THEIR PREPARATIONS, STRENGTHS, AND USAGE

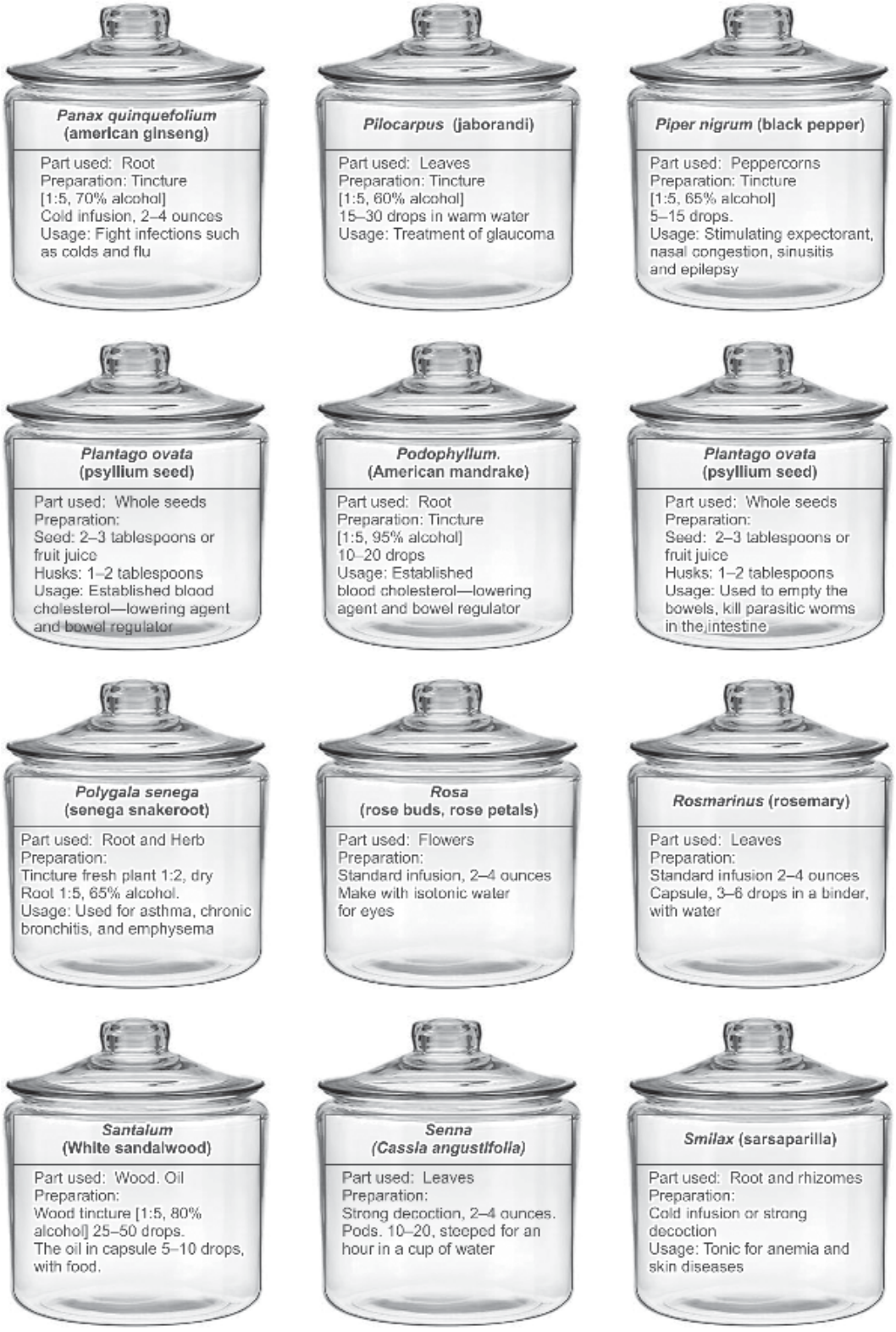


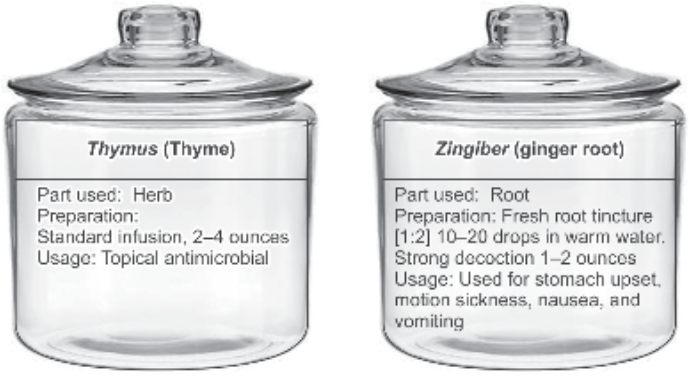

Agrimonia (agrimony)
Part used: Herb
Preparation: Infusion
Dose: Tincture (1:5, 50% alcohol)
1/4 to 1 teaspoon as needed
Allium sativum (garlic)
Part used: Bulb
Preparation: Infusion
Dose: Tincture (1:2)
1/4 to 1 teaspoon as needed
ALOE
(Aloes socrotine)
Part used: Dried juice
Preparation: Herbal capsules
Dose: Tincture
[1:10, 50% alcohol]
Use: Antispasmodic
Amaranthus
(pigweed, alegria)
Part used: Whole plant
Preparation: Standard infusion
Ambrosia (ragweed)
Part used: Herb
Preparation: Standard infusion
Dose: Fresh tincture
[1:2] 20–40 drops
Amygdalis persica
(peach tree)
Part used: Fresh twigs
Preparation: Cold infusion
Dose: Tincture
[1:2] 30–90 drops
Anaphalis margaritacea
(pearly everlasting)
Part used: Flowering herb
Preparation: Standard infusion
Rubbed leaves mixed
with hot water for poultice
Angelica
Part used: Root
Preparation: Tincture
Fresh Root, 1:2, Dry root,
1:5, 65% alcohol
Seed: Tincture, 10–30 drops,
or several seeds chewed
Anisum (anise seed)
Part used: Seed
Preparation: Standard infusion
Spirit of anise, 1/4 to 1/2
teaspoon,
Oil of anise: 1–5 drops
Arnica (*A. montana*)
Part used: Whole plant
Preparation: Flower or root
tincture
Dry root tincture, flowers
herb tincture
Dose: One or two parts of
water or 3–10 drops.
Artemisia vulgaris
(Mugwort)
Part used: Herb
Preparation: Tincture
Standard infusion (drunk hot)
for diaphoretic, cold
infusion as tonic.
Asparagus officinale
Part used: Root
Preparation: Tincture
Fresh, 1:2, Dry, 1:5, 50% alcohol


Balsam of Peru
(Peruvian balsam)
Part used: Resin (dark brown, syrupy)
Preparation: Mix one-part balsam with two parts of lanolin or lard.5–10 drops in capsule.
Balsam of Tolu
(Myroxylum toluiferum)
Part used: Resin (light brown, syrupy, aromatic)
Preparation: Tincture take 15–30 drop doses or add to boiling H_2O for steam inhalation
Baptisia
(Wild indigo root)
Part used: Root, whole plant
Preparation: Fresh tincture 10–25 drops
Berberis vulgaris
(Common barberry)
Part used: Root
Preparation: Tincture [1:5, 50% alcohol]
Cold infusion, 1–3 ounces
Calendula officinalis
(European marigold)
Part used: Flowers
Preparation: Tincture 1:2, dry flowers, 1:5, 70% alcohol.
Usage: Dilute with several parts of water for topical use.
Cannabis sativa
(Marijuana, hemp)
Part used: Flowering tops
Preparation: Tincture
Fresh Herb, 1:2
dry herb, 1:5
5–30 drops
Capsicum
(African bird peppers)
Part used: Fruit
Preparation: Tincture
Fresh herb, 1:5 (15 drops)
Capsules
Cardamomum
(Cardamom seeds)
Part used: Seeds
Preparation: Tincture
Fresh herb, 1:5 (10 drops)
or chew a couple seeds
Carthamus tinctoria
(Saffron)
Part used: Flowers
Preparation:
Standard infusion 4–8 ounces
Usage: Asthma, Cough
***Carum* (caraway seed)**
Part used: Seed
Preparation: Spirit of caraway 10–20 drops in water or some chewed seeds or simple tea for indigestion
***Caryophyllus* (cloves)**
Part used: Unripe buds
Preparation: Capsule
Uses: Cardiotonic
Gastrointestinal disorder


Cassia marilandica (American senna)
Part Used: Leaves
Preparation: Standard infusion contains mixture of ¾ Senna and ¼ Coriander seeds
Uses: Antispasmodic
Centella asiatica (brahmi)
Part used: Herb
Preparation: Fresh Plant Tincture (1:2, 15–30 drops)
Standard infusion
dry herb tincture (1:5, 50% alcohol] 20–40 drops
Cephalanthus (button bush)
Part used: Bark and twings
Preparation: Tincture [Fresh Plant, 1:2, Dry plant, 1:5, 50% alcohol] 10–30 drops
Chrysanthemum parthenium (feverfew)
Part used: Herb
Preparation: Cold infusion 2–4 ounces. Tincture [Fresh plant, 1:2. dry herb, 1:5, 50% alcohol] 30–60 drops
Cinchona (Peruvian bark, quinine bark)
Part used: Bark
Preparation: Cold infusion 2–3 ounces. promoting the release of digestive juices: and treating bloating and fullness.
Cinnamomum (Cinnamon, canela)
Part used: Bark
Preparation: Standard infusion tincture [1:5, 60% alcohol, 5% glycerin] 20–50 drops
Commiphora (myrrh gum)
Part used: Resin
Preparation: Tincture [1:5, 95% alcohol] 5–20 drops.
Capsules
Dilute tincture with water as needed.
Coriandrum (coriander, cilantro)
Part used: Seed
Preparation: Tincture [1:5, 65% alcohol] 10–20 drops
Seeds chewed as needed
Uses: Digestion problems including upset stomach, loss of appetite and nausea
Curcuma (turmeric)
Part used: Root
Preparation: Tincture [1:5, 50% alcohol], 10–30 drops.
Uses: Inflammation; arthritis
Dioscorea villosa (wild yam)
Part Used: Root
Preparation: Fresh root, 1:2, Dry root [1:5, 60% alcohol] 30–100 drops.
Fluid extract [1:1, 55% alcohol] 10–25 drops. Cold infusion, 2–4 ounces
Echinacea angustifolia (purple coneflower)
Part Used: Root and Flowers
Preparation: Tincture [Fresh plant 1:2, Dry plant, 1:5, 70% alcohol]
Cold infusion 2–6 ounces
Fluid extract (1:1, 65% alcohol)
Eucalyptus
Part used: Leaves
Preparation: Standard infusion, 2–4 ounces
Capsule
Uses: Coughs, colds, sore throats, asthma, and congestion


Foeniculum (fennel seed)
Part used: Seed
Preparation: Tincture [1:5, 60% alcohol] 30–60 drops in warm water. Standard infusion
Usage: Various digestive problems including heartburn
Gentiana (gentian)
Part used: Root
Preparation: Tincture [Fresh Root 1:2, dry root, 1:5, 50% alcohol]
Usage: Bitters to stimulate the appetite, improve digestion
Ginkgo biloba (Maidenhair tree)
Part used: Leaves
Preparation: Standard infusion, 2–4 ounces. Tincture [1:5, 60% alcohol)
Usage: Cognitive disorders, dementia, dizziness/ vertigo
Glycyrrhiza glabra (licorice)
Part used: Root
Preparation: Tincture [1:5, 50% alcohol] 3–60 drops. Strong decoction, 1–3 ounces
Usage: Repair of stomach lining and restore balance
Hypericum (St. John's Wort)
Part used: Flowering tops
Preparation: Tincture [Fresh Plant, 1:2] 20–30 drops, Standard infusion, 3–6 ounces
Usage: Effective for mild to moderate depression
Lavandula (lavender)
Part used: Flowers
Preparation: Standard infusion, 2–3 ounces capsule
Usage: Help promote calmness and wellness
Linum (flaxseed)
Part used: Seeds
Only use freshly ground whole seeds internally
Dosage: 1–2 teaspoons in cup of warm water
Mentha piperita (Peppermint)
Part used: Herb
Preparation: Standard infusion 10–20 drops in capsules
Usage: Common cold, cough, inflammation of the mouth
Myristica (nutmeg, mace)
Part used: Seed
Preparation: Tincture [1:5, 75% alcohol] 5–10 drops
Usage: Diarrhea, nausea, stomach spasms and pain
Nymphaea odorata (white pond lily)
Part used: Dried rhizome
Preparation: Strong decoction, 1–2 ounces to 4X a day
Usage: Alternative, anodyne, antiseptic, astringent and demulcent
Olea europaea (olive)
Part used: Leaves
Preparation: Standard infusion, 1–3 ounces
Usage: To prevent heart attack, treat constipation and stroke
Panax ginseng (Asian ginseng)
Part used: Root
Preparation: Tincture [1:5, 70% alcohol].
Usage: Improve thinking, concentration and memory


Panax quinquefolium (american ginseng)
Part used: Root
Preparation: Tincture [1:5, 70% alcohol]
Cold infusion, 2–4 ounces
Usage: Fight infections such as colds and flu
Pilocarpus (jaborandi)
Part used: Leaves
Preparation: Tincture [1:5, 60% alcohol]
15–30 drops in warm water
Usage: Treatment of glaucoma
Piper nigrum (black pepper)
Part used: Peppercorns
Preparation: Tincture [1:5, 65% alcohol]
5–15 drops.
Usage: Stimulating expectorant, nasal congestion, sinusitis and epilepsy
Plantago ovata (psyllium seed)
Part used: Whole seeds
Preparation:
Seed: 2–3 tablespoons or fruit juice
Husks: 1–2 tablespoons
Usage: Established blood cholesterol—lowering agent and bowel regulator
Podophyllum. (American mandrake)
Part used: Root
Preparation: Tincture [1:5, 95% alcohol]
10–20 drops
Usage: Established blood cholesterol—lowering agent and bowel regulator
Plantago ovata (psyllium seed)
Part used: Whole seeds
Preparation:
Seed: 2–3 tablespoons or fruit juice
Husks: 1–2 tablespoons
Usage: Used to empty the bowels, kill parasitic worms in the intestine
Polygala senega (senega snakeroot)
Part used: Root and Herb
Preparation:
Tincture fresh plant 1:2, dry Root 1:5, 65% alcohol.
Usage: Used for asthma, chronic bronchitis, and emphysema
Rosa (rose buds, rose petals)
Part used: Flowers
Preparation:
Standard infusion, 2–4 ounces
Make with isotonic water for eyes
Rosmarinus (rosemary)
Part used: Leaves
Preparation:
Standard infusion 2–4 ounces
Capsule, 3–6 drops in a binder, with water
Santalum (White sandalwood)
Part used: Wood. Oil
Preparation:
Wood tincture [1:5, 80% alcohol] 25–50 drops.
The oil in capsule 5–10 drops, with food.
Senna (*Cassia angustifolia*)
Part used: Leaves
Preparation:
Strong decoction, 2–4 ounces. Pods. 10–20, steeped for an hour in a cup of water
Smilax (sarsaparilla)
Part used: Root and rhizomes
Preparation:
Cold infusion or strong decoction
Usage: Tonic for anemia and skin diseases



ORGAN SYSTEM ENERGETICS

Herbal formulation effect absorption, metabolism, fluid transport and excretion. It also effects function (physiology) not structure (anatomy).

- Excess means organ system is over functioning, usually from hormonal or neurologic causes.
- Deficiency result from the lifelong accommodations between inherited organ strengths and weaknesses.

	Excess/deficiency	Herbs stimulate/cool
	Upper GI deficiency symptoms: Dry mouth, usually with a history of gum and teeth problems.	**Herbs stimulates:** Act as bitter tonic administrated before meals, accumulating both mouth and gastric juices to boost better function. Stimulate function by exciting membrane secretions. Increasing blood supply to the mouth, stomach and pancreas.
	Symptoms of upper GI excess: Moist mouth and oversecreting stomach in the presence of food, red-tipped tongue and an embellished and rapid emptying of the stomach and bowels in the morning.	**Herbs cool:** Act as an astringent, protectant or anesthetic to the muscle coats and mucosa.
	Lower GI deficiency symptoms: Simple constipation, with poor stimulation of colon function, dehydration, extended transit time and the long-term tendency to overlook the defecation reflex.	**Herbs stimulates:** Increase bile and pancreatic secretions. May rise peristalsis by direct irritation, vasodilation or parasympathetic stimulation.
	Lower GI excess: Rapid transit of food through the GI tract with dark soft stools and heightened defecation reflex.	**Herbs cool:** Sedate plexus nerves in the smooth muscle walls, suppress parasympathetic excess, cool the thyroid, or act as simple astringents.

(contd.)

Excess/deficiency	Herbs stimulate/cool
Liver deficiency symptoms: Dry skin and mucosa Atopic allergies of the skin Sinuses and bronchial mucosa Poor fat and protein metabolism and appetite.	**Herbs stimulate:** Increase liver metabolism by exciting hepatocyte enzyme production, increasing bile synthesis and liver cleansing, improving fat absorption into the lymph, or increasing blood supply by dilating the hepatic artery.
Liver excess symptoms: Moist, oily skin; fat and protein cravings, hyperuricemia and essential hypertension, rapid defense response with quick fever and sweating.	**Herbs cool:** Increase blood buffering of nitrogen compounds with electrolytes, increase bile secretion without stimulating liver metabolism, or aid in sodium loss/potassium retention.
Kidney deficiency symptoms: Dilute and pale urination, flushing, thirst and the tendency for low blood pressure.	**Herbs stimulate:** Strengthen or stimulate kidney nephrons, improve renal blood supply, adrenalin stress, and improve hormonal stimulation.
Kidney excess symptoms: Sodium and water retention, essential hypertension, and orthostatic hypertension.	**Herbs cool:** Dilate renal arteries, relax the limbic system and the hypothalamus, decrease tubular reabsorption of sodium or decrease water reabsorption by altering osmosis in the nephrons, with sodium.
Reproductive deficiency in women: Long cycles, erratic cycles; menses that start slowly, with cramping and spotting and that extend too long.	**Herbs stimulate (in both sexes):** Increase utilization of steroids, improve pelvic circulation, or effect the hypothalamus/pituitary relationship.
Reproductive excess symptoms: In women short estrus cycle with a rapid peaking of estrogen after menses.	**Herbs cool:** Liver excess, modifying the diet and methods of diminishing pituitary/hypothalamic stress are more useful.
Respiratory deficiency symptoms: Lung problems, shortness of breath, dry membranes with poor expectoration, frequent yawning and noticeably labile respiration.	**Herbs stimulate:** Increase in cardiopulmonary function or counterbalance adrenalin stress by increasing parasympathetic function.
Respiratory excess symptoms: Hyperventilate under stress, have active and excessive expectoration, or have the type of moderate cardiopulmonary excitation associated with thyroid stress.	**Herbs cool:** Cooling liver and mucus membrane functions or lessening the causes cardiovascular excess will take care of the limited secondary effects of respiratory heat.
Cardiovascular deficiency symptoms: Cold hands and feet, dry skin and mucosa, and shallow pulse that is often quick and easily compressed.	**Herbs stimulate:** Increase the force and efficiency of cardiac output, increase the resilience of arterial walls, stimulate parasympathetic energy or act as simple vasodilators.

(Contd.)

Excess/deficiency	Herbs stimulate/cool
Cardiovascular excess symptoms: Warm skin, bounding pulse, strong and easy secretions and excretions. This is usually concurrent with varying degrees of essential hypertension with excess blood and interstitial fluid.	**Herbs cool:** Support parasympathetic or cholinergic energies, sedate the heart and major arteries or act as sodium leaching diuretics.
Lymph/immune deficiency symptoms: Chronic moderate immunodeficiency; slow recuperation, slow healing of injuries and bruises, frequent low level infections in high-stress tissues such as the respiratory mucosa and skin, and cold and flu symptoms that come and go for a month or more.	**Herbs stimulate:** Increase efficiency of lymph transport, the bone marrow proliferation of WBCs, phagocytosis by innate immunity granulocytes, and overall synthesis of blood immunoglobulins and complement protein by the liver. Some tonics stimulate liver breakdown of immune waste products as well.
Skin/mucosa deficiency symptoms: Liver deficiency. Dry flaky skin, with crack and fissures, eczema and strange rough spots are typical, as well as frequent mouth, rectal and vaginal sores or inflammation.	**Herbs stimulate:** Increase blood supply, stimulate cholinergic sympathetic and parasympathetic enervation, or support the liver (and related functions) to make better quality proteins and fats for cell regeneration.
Skin/mucosa excess symptoms: Greasy and oily skin, often with adolescent type acne (acne vulgaris). All the skin is oily, not just the face, and all the skin is moist, not just the face, neck, hands and feet (an adrenalin-induced sweat).	**Herbs cool:** Sedative to skin nerves or decrease liver excitability. Skin/mucosa excess is usually dependent on reproductive, liver and kidney excess and hard to effect directly.
Muscle/skeletal deficiency symptoms: Joint aches and sense of weakness in the shoulder or legs. Much chronic joint and muscle pain have little constitutional implication and needs to be treated separately.	**Herbs stimulate:** Sympathetic and motor nerve tonics or help to increase blood flow to the muscles and joints.
Muscle/skeletal excess symptoms: Tight muscles and tendons in the neck, back and legs.The most pronounced excess is in the muscles most effected by adrenalin, those of the neck, shoulders, intercostal, lower back, and legs.	**Herbs cool:** Oppose adrenergic stress, disperse blood to the viscera or act as simple muscle relaxers.

Herbal medicinal plants for natural well-being

Adaptogen herbs
Ashwaganda (Withania somnifera)
Astragalus (Astragalus membranaceus)
Codonopsis (Codonopsis pilosula)
Ginseng (Panax ginseng)
Holy Basil (Ocimum sanctum)
Licorice (Glycerhiza glabra)
Rhodiola (Rhodiola rosea)
Schizandra (Schizandra chinensis)
Shatavari (Asparagus racemosus)

Antimicrobial herbs
Bee balm (Monarda fistulosa)
Cedar (Thuja occidentalis)
Elderberry (Sambucus nigra)
Yarrow (Achillea millefolium)
Elecampane (Inula helenium)
Garlic (Allium sativum)
Goldenseal (Hydrastis canadensis)
Juniper (Juniperus communis)
Oregon Grape Root (Mahonia aquifolium)
Rosemary (Rosmarinus officinalis)
St. John's Wort (Hypericum perforatum)
Usnea (Usnea spp.)

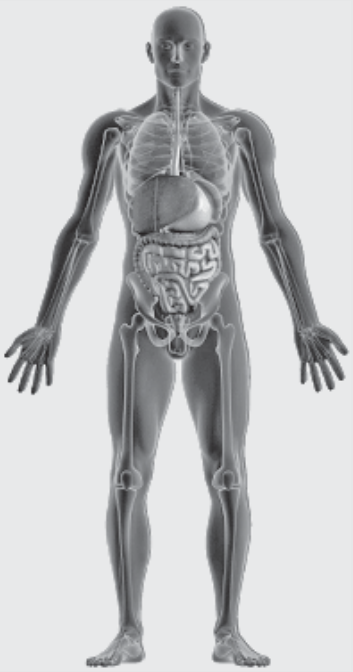
Antihelminthic herbs
Bee balm (Monarda fistulosa)
Black Walnut (Juglans nigra)
Garlic (Allium sativum)
Ginger (Zingiber officinale)
Wormwood (Artemisia absinthium)

Bitters
Artichoke leaf (Cynara cardunculus)
Boneset (Eupatorium perfoliatum)
Centaury (Centaurium erythraea)
Chamomile (Matricaria recutita)
Dandelion leaf (Taraxacum officinale)
Gentian root (Gentiana lutea)
Goldenseal (Hydrastis canadensis)
Horehound (Marrubium vulgare)
Oregon Grape Root (Mahonia aquifolium)
Yarrow (Achillea millefolium)

Cardio tonic herbs
Hawthorne (Craetagus spp.)
Linden (Tilia spp.)
Arjuna (Terminalia arjuna)
Motherwort (Leonurus cardiaca)

Alternative herbs
Burdock (Arctium lappa)
Cleavers (Galium aparine)
Dandelion root (Taraxacum officinale)
Echinacea (Echinacea purpurea)
Goldenseal (Hydrastis canadensis)
Red Root (Ceonothus spp.)

Anodyne herbs
Arnica (Arnica montanum)
Belladonna (Atropa belladonna)
Cottonwood (Populus spp.)
Essential oils (Clove and cinnamon)
Ginger (Zingiber officinale)
St. John's Wort (Hypericum perforatum)
Yarrow (Achillea millefolium)



Cholagogue herbs
Artichoke leaf (Cynara scolymus)
Dandelion root (Taraxacum officinale)
Fumitory (Fumaria officinalis)
Gentian (Gentiana lutea)
Oregon Grape Root (Mahonia aquifolium)
Celandine (Chelidonium majus)
Yellow dock (Rumex crispus)

Anti-inflammatory herbs
Celery seed (Apium graveolens)
Chickweed (Stellaria media)
Gotu Kola (Centella asiatica)
Hawthorn (Craetagus spp.)
Lavender (Lavendula spp.)
Willow (Salix spp.)
Licorice (Glycyrrhiza glabra)
Linden (Tilia spp.)
Marshmallow (Althaea officinalis)
Meadowsweet (Filipendula ulmaria)
Paprika (Capsicum annuum)
Plantain (Plantago lanceolata. P. major)
Turmeric (Curcumin longum)
Ginger (Zingiber officinale)

Antispasmodic herbs
Black cohosh (Cimicifuga racemosa)
California poppy (Eschscholzia californica)
Chamomile (Matricaria recutita)
Cramp bark (Viburnum opulus)
Ginger (Zingiber officinalis)
Jamaica dogwood (Piscidia erythrina)
Kava (Piper methysticum)
Lemon balm (Melissa officinalis)
Lobelia (Lobelia inflata)
Motherwort (Leonurus cardiaca)
Passionflower (Passiflora incarnata)
Skullcap (Scutellaria lateriflora)
Valerian (Valeriana officinalis)
Wild Cherry Bark (Prunus spp.)
Wild lettuce (Lactuca virosa)
Wild yam (Dioscorea villosa)

Astringent herbs
Agrimony (Agrimonia eupatoria)
Black berry (Rubus spp.)
Goldenrod (Solidago spp.)
Many rose family plants
Horse chestnut (Aesculus hippocastanum)
Oak bark (Quercus spp.)
Raspberry (Rubus Idaeus)
Shepherd's purse (Capsella bursa-pastoris)
Uva ursi (Arctostaphylos uva ursi)
Witch hazel (Hamamelis virginiana)

Carminative herbs
Angelica (Angelica archangelica)
Bee balm (Monarda fistulosa)
Cardamom (Elettaria cardamommum)
Chamomile (Matricaria recutita)
Fennel (Foeniculum vulgare)
Ginger (Zingiber officinale)
Mints (Mentha pipreta)
Parsley (Petroselinum crispum)
Thyme (Thymus vulgaris)

CHAPTER **10**

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Handbook of **Herbal Formulation**

Herbal formulations play a significant role in maintaining health. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. Novel herbal formulations have various advantages over the traditional formulations such as improved solubility and bioavailability, reduced toxicity, controlled drug delivery, protections of plant actives from degradation.

This book comprises many units — the first unit is well laid out and sequentially explores relevant topics like herbal formulation, definitions, classification, traditional vs modern herbal formulation and herbal dosage forms.

The details about formulation consideration of herbal dosage form, it provides number of examples of herbal excipient like colorants, flavouring agent with their evaluation guidelines. The chapter also contains comparison between herbal conventional formulation as well as herbal novel drug delivery.

Chapter 4 focuses on intellectually property rights and patenting of herbal formulations covering concepts of IPR, regulatory issues and documentation of patenting herbal formulations. The information presented in Chapters 5 and 6 primarily deal with nutraceuticals and cosmeceuticals herbal based formulation. Chapter 5 provides information on health benefits of nutraceuticals, regulatory requirements and worldwide scenario of nutraceuticals.

The next informative topics are evaluation of quality, efficacy and safety of herbal formulation, their quality consideration, efficacy assessment and safety concern of herbal formulation. The concise text containing status of herbal formulation related to trading, export and import, global market of herbal formulation. The relevant piece of information is herbal drugs commonly used for formulation developments including name of drug, active constituents and pharmacological efficacy.

In addition, book contains specific text on bioavailability of herbals, mechanism of action, ideal property of bioenhancer and herbs, source, mechanism and their dose as bioenhancers. The current need is pharmacovigilance of herbal medicines, challenges in monitoring safety of herbal medicines and WHO drug monitoring program.

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